Multimodal pain management after arthroscopic surgery

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MULTIMODAL PAIN MANAGEMENT AFTER ARTHROSCOPIC SURGERY

BY
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AALBORG UNIVERSITY
DENMARK

MULTIMODAL PAIN MANAGEMENT AFTER ARTHROSCOPIC SURGERY

by

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Dissertation submitted

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CV

Sten Rasmusen is associated professor in orthopaedic surgery at Aalborg University Hospital. SR is head of research within sports medicine and arthroscopy. Since November 2011 SR is head of the spearhead function "Motivated and maintained running, evidence based supported" at Aalborg University Hospital. The main research topics are multimodal pain treatment, musculoskeletal pain and running related injuries.

There have been many years of research effort directed at the optimal clinical pathway targeted the causality between intervention and surgical pathophysiology against outcome. The interventions being preoperative information and training, minimal invasive surgery, multimodal pain management and early mobilization.

Several studies present different aspect of musculoskeletal pain. More than 10 publications investigate different aspects of running related injuries and pain. One study found no increased risk of injury in 931 novice runners using a neutral running shoe. More than 10 publications investigate patellofemoral pain in 3000 adolescents. One study finds that half of 12-15 years old still have pain after one year. Further musculoskeletal pain is studied using conditioned pain modulation and quantitative sensory testing in osteoarthritis, patellofemoral pain in adolescents, total knee arthroplasty, lumbar spondylodesis, ankle sprain hip fracture and healthy volunteers.

In June 2015 Sten Rasmussen completed the Harvard Medical School Global Clinical Scholars Research Training Program (GCSRT) with commendation for the Capstone Project Proposal.

ENGLISH SUMMARY

Pain, convalescence and recovery are direct consequences of the surgical stress response during and after orthopaedic surgery. Different analgesic strategies aim at relieving pain as the primary treatment goal. Why is functioning and wellbeing not more important? We questioned whether pain treatment could influence recovery after arthroscopic surgery, hypothesised that multimodal pain treatment would provide a faster recovery after arthroscopic surgery and aimed to conduct a series of double blind placebo-controlled randomised trials of different analgesic treatment modalities after knee and ankle arthroscopy to test those hypotheses.

Prior to our research start, no information was available within orthopaedic surgery on the surgical stress-reducing possibilities and pain reducing capacities of anti-inflammatory drugs (NSAIDs), multimodal intra-articular pain treatment or multimodal intervention. In order to modulate and reduce this surgical stress response and subsequent pain to provide a faster recovery, we planned to study the effect of unimodal and multimodal intervention in arthroscopic surgery. We planned to study the unimodal effect of NSAIDs and secondly, the multimodal intra-articular pain treatment.

In order to investigate the clinical effect of naproxen sodium on recovery, measured primarily as days until return to work after arthroscopy of the knee, 120 patients were randomised to either 550 mg naproxen sodium twice daily or placebo for 10 days.

In order to investigate the effect of intra-articular methylprednisolone plus morphine plus bupivacaine versus morphine plus bupivacaine or saline on recovery, measured primarily as time taken to return to work after arthroscopic knee meniscectomy, 60 patients were equally randomised into three groups.

In order to investigate the effect of intra-articular methylprednisolone plus morphine plus bupivacaine versus morphine plus bupivacaine or saline on recovery, measured primarily as time taken to return to work after diagnostic knee arthroscopy, 60 patients were equally randomised into three groups.

In order to investigate the effect of intra-articular methylprednisolone plus morphine plus bupivacaine versus saline on recovery, measured primarily as time taken to return to work after arthroscopic ankle debridement for impingement, 36 patients were equally randomised into two groups.

Time to return to work was reduced in all four trials at a statistically significant level. NSAIDs for 10 days after knee arthroscopy reduced time to return to work

from 17 (11-31) to 14 (10-31) days. Intra-articular treatment with morphine plus bupivacaine or methyl-prednisolone plus morphine plus bupivacaine after arthroscopic knee meniscectomy reduced time to return to work from 10 (1-30) to 5 (1-14) to 3 (0-13) days. Intra-articular treatment with morphine plus bupivacaine or methylprednisolone plus morphine plus bupivacaine after diagnostic knee arthroscopy reduced time to return to work from 10 (1-14) to 5 (1-10) to 2 (0-15) days. Intra-articular treatment with methylprednisolone plus morphine plus bupivacaine after arthroscopic ankle debridement for impingement reduced time to return to work from 7 (1-52) to 2 (1-21) days.

Hours of walking activity, use of crutches in days, days until pain-free, range of motion, synovial joint effusion and muscular strength were all to some extent influenced by active treatment in the four trials by a statistically significant amount.

Additional analysis revealed that the surgical trauma influenced range of motion, synovial joint effusion and muscular strength by a statistically significant amount and that avoiding use of a tourniquet accelerated time to return to work by 4.88 (3.01 – 6.75) days, a statistically significant amount.

In the four trials, we have demonstrated a shorter duration of convalescence of several days with a reduction in the time to return to work after knee and ankle arthroscopy with the use of oral NSAIDs combined with bupivacaine plus morphine or combined with bupivacaine, morphine plus steroid.

DANSK RESUME

Smerte, rekonvalescens og bedring tilbage til normal aktivitet er direkte konsekvenser til det kirurgiske stress respons under og efter ortopædkirurgiske operationer. Forskellige analgetiske behandlings strategier stræber efter som primært mål er at lindre smerten. Men hvorfor er funktion og velvære ikke mere vigtig? Vi satte spørgsmål ved, om ikke smertebehandling kan bedre tilbagevenden til normal aktivitet efter artroskopisk kirurgi, vi antog at multimodal smerte-behandling kan afkorte bedring efter artroskopisk kirurgi og satte målet at gennemføre en dobbelt blinde placebo kontrollerede forsøg med forskellige analgetiske behandlings modaliteter efter knæ og ankel artroskopi.

Forud for forskningsprojektets start var der ikke nogen tilgængelig viden indenfor ortopædisk kirurgi om kirurgisk stress reducerende muligheder eller smertereduktion med brug af non-steroide anti-inflammatoriske præparater (NSAIDs), multimodal intraartikulær smertebehandling eller multimodal intervention.

For at modulere og reducere det kirurgiske stress respons og den efterfølgende smerte med henblik på at afkorte bedring planlagde vi at studere effekten af unimodal og multimodal intervention efter artroskopisk kirurgi. Vi planlage at undersøge den unimodale effekt af NSAID og efterfølgende en multimodal intraartikulær smertebehandling.

For at undersøge den kliniske effekt af naproxen natrium på bedring målt som antal dage indtil genoptaget arbejde efter knæ artroskopi blev 120 patienter randomiseret til enten naproxennatrium 550 mg to gange dagligt eller placebo i 10 dage.

For at undersøge den kliniske effekt af intraartikulær methyl-prednisolon plus morfin plus bupivacain versus morfin plus bupivacain eller placebo på bedring målt som antal dage indtil genoptaget arbejde efter artroskopisk knæ menisk resektion blev 60 patienter ligeligt randomiseret til tre grupper.

For at undersøge den kliniske effekt af intraartikulær methyl-prednisolon plus morfin plus bupivacain versus morfin plus bupivacain eller placebo på bedring målt som antal dage indtil genoptaget arbejde efter diagnostisk knæ artroskopi blev 60 patienter ligeligt randomiseret til tre grupper.

For at undersøge den kliniske effekt af intraartikulær methyl-prednisolon plus morfin plus bupivacain versus morfin plus bupivacain eller placebo på bedring målt som antal dage indtil genoptaget arbejde efter artroskopisk debridement af ankelled impingement blev 36 patienter ligeligt randomiseret til to grupper.

Tilbagevenden til arbejde blev statistisk signifikant reduceret i alle fire forsøg. NSAID givet i 10 dage efter knæ artroskopi reducerede tilbagevenden til arbejde fra 17 (11-31) til 14 (10-31) dage. Intraartikulær behandling med morfin plus bupivacain eller methylprednisolon plus morfin plus bupivacain efter artroskopisk knæ menisk resektion reducerede tilbagevenden til arbejde fra 10 (1-30) til 5 (1-14) til 3 (0-13) dage. Intraartikulær behandling med morfin plus bupivacain eller methylprednisolon plus morfin plus bupivacain efter diagnostisk knæ artroskopi reducerede tilbagevenden til arbejde fra 10 (1-14) til 5 (1-10) til 2 (0-15)dage. Intraartikulær behandling med methylprednisolon plus morfin plus bupivacain efter artroskopisk debridement af ankelled impingement reducerede tilbagevenden til arbejde fra 7 (1-52) til 2 (1-21) dage.

Antal timer gående aktivitet, brug af krykker i dage, dage indtil smertefri, bevægeudslag, led ansamling og muskelstyrke blev i de fleste tilfælde statistisk signifikant påvirket af den aktive intervention i alle fire forsøg.

Yderligere analyse af data afslørede at det kirurgiske traume statistisk signifikant påvirkede bevægeudslag, led ansamling samt muskelstyrke og at ingen brug af blodtomhed statistisk signifikant reducerede tilbagevenden til arbejde med 4.88 (3.01 – 6.75) dage.

I de fire forsøg har vi påvist en længerevarende effekt på flere dage med reduktion i tilbagevenden til arbejde efter knæ og ankel artroskopi med brug af NSAID kombineret med morfin plus bupivacain eller steroid plus morfin plus bupivacain.

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I am deeply grateful to Professor Henrik Kehlet, M.D., DM.Sc., and Ole H. Simonsen, M.D., DM.Sc., for introducing me to clinical science and for their patience and confidence in me. In particular, I am much obliged to Professor Henrik Kehlet who acknowledged, understood and structured my research questions. Further, Professor Henrik Kehlet guided me with a strong hand through the clinical randomised trials.

I would like to extend my sincere thanks to the patients and staff from Hjørring and Hvidovre Hospitals. This thesis would not have been possible without their generous participation.

During my actual appointment at the Department of Orthopaedic Surgery and Orthopaedic Surgery Research Unit, Aalborg University Hospital, this thesis was completed. I am deeply grateful to the Department of Orthopaedic Surgery giving me the time and support to complete this thesis.

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For many of the translational promising ongoing and new studies extending from the current trials, I am much indebted to my group of younger researchers: Ren Gang, Michael Rathleff, Rasmus Østergaard Nielsen, Ashir Ejaz, Peter Larsen, Søren Thorgaard Skou, Marius Aliuskevicius, Vesal Khalid, Rene Korsgaard Brund, Michael Lejbach Bertelsen, Rasmus Elsøe, Daniel Ramskov, Camma Damsted, Torben Rokkedal Lausch, Jesper Petersen and Dennis Pedersen.

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Associate Professor Jens Lykkegaard Olesen, Department of Rheumatology, Aalborg University Hospital.

Professor Martin Lind, Professor Erik T. Parner and Associate Professor Henrik Sørensen, Aarhus University.

Professor Ewa Roos and Professor Ellen Aagaard Nøhr, Odense University.

Professor Henning Langberg, Copenhagen University.

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..... Without passion no change, without change no view!

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CHAPTER 1. PREFACE

The current Ph.D. thesis was submitted as part of the requirements for attaining the Ph.D. degree at the Faculty of Medicine and The Doctoral School in Medicine, Biomedical Science and Technology, University of Aalborg.

The research for this thesis was carried out from 1990 to 2000 during my appointments as surgeon at the Department of Orthopaedic Surgery, Hjørring Hospital, and the Department of Orthopaedic Surgery, Copenhagen University Hospital in Hvidovre.

The following papers and additional analyses based on the dataset from these randomised controlled trials formed the basis for this thesis:

I. Rasmussen S, Thomsen S, Madsen SN, Rasmussen PJS, Simonsen OH. The Clinical Effect of Naproxen Sodium after Arthroscopy of the Knee. Arthroscopy 1993; 9: 375-80.

II. Rasmussen S, Larsen AS, Thomsen ST, Kehlet H. Intra-articular glucocorticoid, bupivacaine and morphine reduces pain, inflammatory response and convalescence after arthroscopic meniscectomy. Pain 1998; 78: 231-4.

III. Rasmussen S, Lorentzen JS, Larsen AS, Thomsen ST, Kehlet H. Combined intra-articular glucocorticoid, bupivacaine and morphine reduces pain and convalescence after diagnostic knee arthroscopy. Acta Orthop Scand 2002; 73: 175-8.

IV. Rasmussen S, Kehlet H. Intraarticular glucocorticoid, bupivacaine and morphine reduces pain and convalescence after arthroscopic ankle surgery. Acta Orthop Scand 2000; 71: 301-4.

CHAPTER 2. INTRODUCTION

2.1. BACKGROUND AND SYNOPSIS

Pain, convalescence and recovery are direct consequences of the surgical stress response during and after orthopaedic surgery (Figures 1 and 2). Different analgesic strategies aim at relieving pain as the primary treatment goal. Why are function and wellbeing not more important? We questioned whether pain treatment could reduce the duration of convalescence after arthroscopic surgery, we hypothesised that multimodal pain treatment would provide faster recovery after arthroscopic surgery, and we aimed at performing a series of double blind placebo-controlled randomised trials of different analgesic treatment modalities after knee and ankle arthroscopy to test those hypotheses.

Prior to our study start, no information was available within orthopaedic surgery on the surgical stress-reducing possibilities and pain-reducing capacities of non-steroidal anti-inflammatory drugs (NSAIDs), multimodal intra-articular pain treatment or multimodal intervention. In order to modulate and reduce the surgical stress response and subsequent pain to provide faster recovery, we planned to study the effect of unimodal, and multimodal intervention in arthroscopic surgery and subsequently do translational research in other orthopaedic procedures.

To the best of our knowledge, we are the first to perform studies on short duration treatment with NSAIDs after knee arthroscopy, combined intra-articular treatment with steroid, morphine and bupivacaine after knee and ankle arthroscopy (I-IV) and multimodal intervention after hip fracture and hip and knee arthroplasty and spine surgery (1-6) (Table 1.1).

Unimodal effect of NSAIDs (I)	04/90 to 04/92
Multimodal intraarticular pain treatment (II-IV)	10/93 to 08/97
	10/93 to 02/00
	10/97 to 12/98
Multimodal intervention (1-4)	03/99 to 12/00
	02/00 to 10/00
	04/99 to 05/01
	05/01 to 08/03
Safety study of local infiltration (5)	06/10 to 11/10
Use of tourniquet study (6)	06/11 to 06/13

Table 1.1 Inclusion periods of patients in the studies.

Prostaglandins, bradykinins, leucotrienes, histamine and serotonins, liberated locally because of tissue damage, mediate post-arthroscopic effusion and synovitis (Figure 2.1). Pain and swelling are direct consequences. Convalescence and recovery after arthroscopy are also dependent on this cascade response.

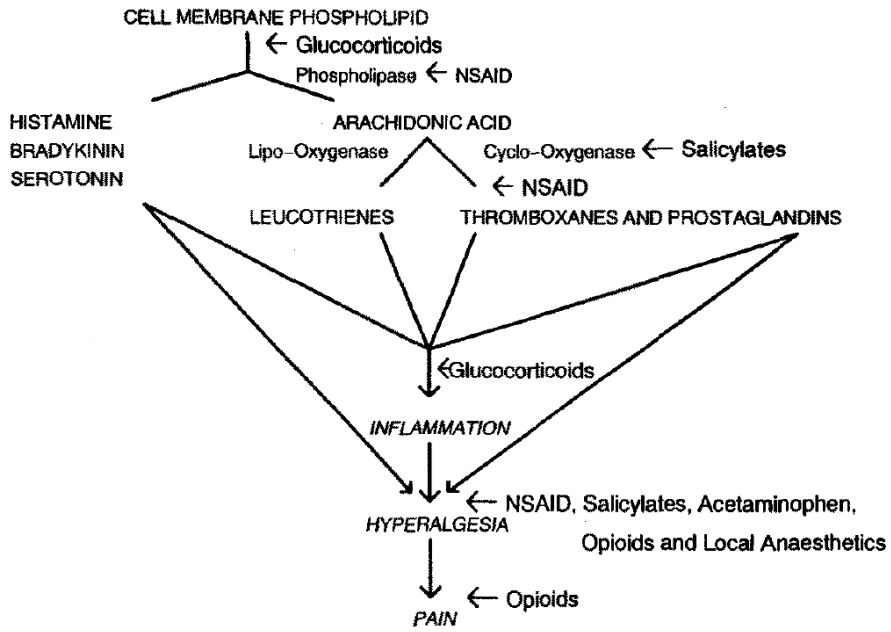

Figure 2.1 The action of NSAIDS and other medications on the inhibition of prostaglandins, inflammation, and pain. (Rasmussen 1993(I))

Factors in the surgical stress response with endocrine-metabolic and inflammatory changes relate to complications after surgery (Figure 2.2) (7-11). In order to prevent these complications, it is important to understand the stress reaction of each organ system.

Minimal invasive surgical technique or pre-operative administration of high-dose steroids may prevent the inflammatory response. Neural blockade is best for prevention of the endocrine-metabolic response. Unimodal intervention cannot eliminate morbidity and mortality after major surgery. Thus, multimodal intervention with attenuation of the surgical stress response, effective dynamic treatment of pain, enforced mobilisation, and nutrition should be employed where possible (Figure 2.3).

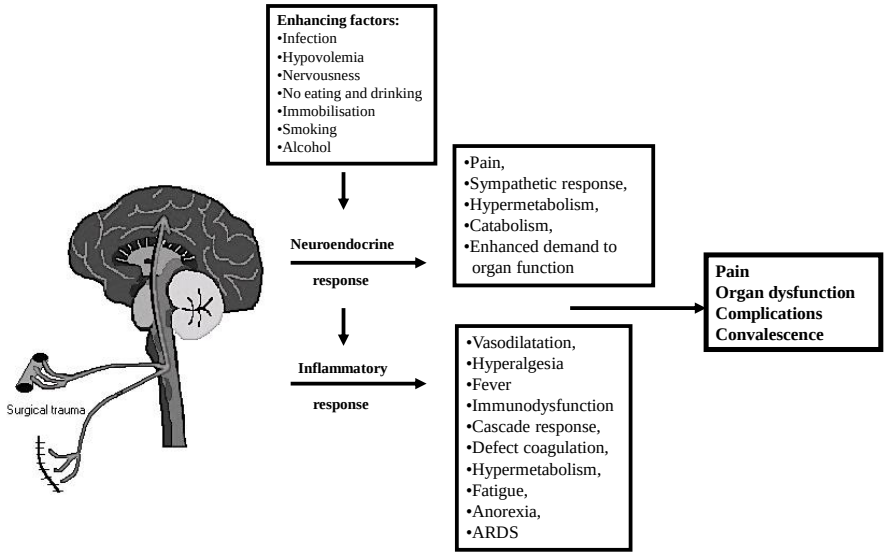

Figure 2.2 The surgical stress response

Pain is the main reason for staying overnight in hospital after arthroscopic surgery and the main reason for not getting out of bed the day after major orthopaedic surgery. Pain is the dominant complaint during convalescence and the cause of unexpectedly long absences from work or recreational activities. Recovery following convalescence is dependent upon the efficacy of treatment where stress reduction, pain treatment and early mobilisation are important factors.

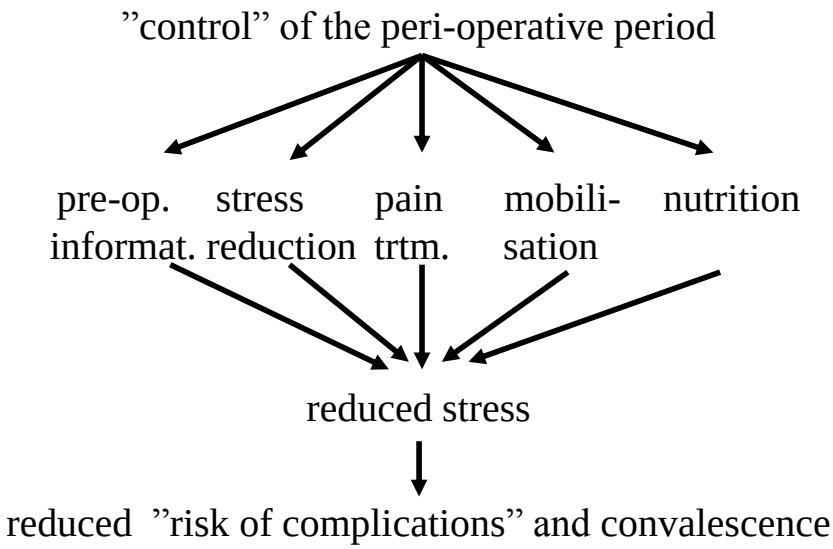

Figure 2.3 Control of the peri-operative period using pre-operative information, stress reduction, pain treatment, early mobilisation and nutrition

The purpose of this thesis was to investigate whether the patterns and modalities of multimodal pain treatment after arthroscopic surgery would result in a faster recovery.

2.2. RESEARCH QUESTION

Can pain treatment influence recovery after arthroscopy?

2.3. HYPOTHESIS

1. Naproxen sodium provides positive clinical effects compared to placebo after *knee arthroscopy*.
2. Multimodal intra-articular pain treatment with (a) methylprednisolone, morphine and bupivacaine is superior in reducing the duration of convalescence compared to (b) morphine and bupivacaine, which is again superior to (c) placebo after *arthroscopic knee meniscectomy*.
3. Multimodal intra-articular pain treatment with (a) methylprednisolone, morphine and bupivacaine is superior in reducing the duration of convalescence compared to (b) morphine and bupivacaine, which is again superior to (c) placebo after *diagnostic knee arthroscopy*.
4. Multimodal intra-articular pain treatment with (a) methylprednisolone, morphine and bupivacaine is superior to (b) placebo in reducing the duration of convalescence after *arthroscopic ankle surgery*.

2.4. AIMS

To test the hypotheses above by conducting the following clinical trials:

1. A randomised, double blind, placebo-controlled two-arm trial of post-operative naproxen sodium after knee arthroscopy.
2. A randomised, double blind, placebo-controlled three-arm trial of intra-articular methylprednisolone plus morphine plus bupivacaine, morphine plus bupivacaine, or saline after arthroscopic knee meniscectomy.
3. A randomised, double blind, placebo-controlled three-arm trial of intra-articular methylprednisolone plus morphine plus bupivacaine, morphine plus bupivacaine, or saline after diagnostic knee arthroscopy.
4. A randomised, double blind, placebo-controlled two-arm trial of intra-articular methylprednisolone plus morphine plus bupivacaine after arthroscopic ankle surgery.

Two hundred and seventy-eight patients participated in the four trials (I-IV). After publication, we deleted patient identifiers from the data. The remaining research data of all 278 patients remained suitable for the Post Arthroscopic Pain Study (PAPS) dataset. In additional analyses of the dataset, we answered the question: ‘Do we have evidence of confounding or effect modification influences due to type of surgery, use of a tourniquet and type of intra-articular analgesia on recovery after arthroscopic surgery?’

CHAPTER 3. METHODOLOGICAL CONSIDERATIONS

3.1. TREATMENT WITH NSAIDS

There was a considerable risk of side effects related to the use of NSAIDs in the late 1980s (12-16). One study found significantly more side effects in patients receiving NSAIDs for 6 weeks after arthroscopic surgery. Using NSAIDs compared to placebo, there was up to four times higher incidence of gastric side effects, heartburn and headache, with cardiovascular events being the most feared (16). Further, 6 weeks of treatment seems out of proportion for minor surgery such as knee arthroscopy. We planned a randomised controlled trial of 10 days treatment with NSAIDs compared to placebo, thereby potentially reducing these side-effects. We evaluated the time before returning to work as the primary measure of the duration of convalescence and hours of walking activity, muscular strength, range of motion, synovial effusion, and use of crutches together with pain profiles as appropriate secondary measures of recovery.

3.2. MULTIMODAL INTRA-ARTICULAR TREATMENT

NSAIDs (I, 12-17) and intra-articular bupivacaine or morphine can reduce post-arthroscopic pain, but do not eliminate pain, inflammatory response or the duration of convalescence (18-20). The use of systemic administration of steroids may reduce inflammatory response and pain after dental surgery and abdominal surgery (21-24). Local intra-articular injections of steroids have been widely used for decades in various rheumatic diseases but no information was available on the use of intra-articular steroid after arthroscopic procedures (25). We planned three randomised controlled trials of combined intra-articular treatment with steroid, morphine and marcain, compared to morphine and marcain or placebo after arthroscopic knee and ankle surgery. We evaluated the time before returning to work as a measure of the duration of convalescence and hours of walking activity, quadriceps strength, range of motion, synovial effusion and use of crutches together with pain profiles as appropriate secondary measures of recovery.

3.3. SURGERY, TOURNIQUET AND ANALGESIA

The key pathogenic factor is the surgical stress response with subsequent increased demands on organ function (Figure 2). This is mediated by the trauma-induced neuro-endocrine and inflammatory metabolic changes and activation of several biological cascade systems (Figure 3.1).

The pathogenesis of postoperative morbidity relates to the various components of the surgical stress response. In arthroscopy, the types of surgery and the use or not of a tourniquet are components of the pathogenesis of post-operative morbidity that may influence outcome.

We performed an additional analysis to evaluate the confounding or effect modification influences of type of surgery, use of a tourniquet and type of intra-articular analgesia on recovery after arthroscopic surgery.

3.4. PAIN

Different orthopaedic procedures have their own characteristic pain pattern and need different analgesic treatment. Detailed information on multimodal pain treatment with the use of intra-articular pain treatment in combination with NSAIDS in arthroscopy and detailed information of multimodal pain treatment in combination with epidural analgesia in major orthopaedic surgery was not available prior to our study start but now is (1, 16). To our best knowledge, we are the first to study and assess the effect of post-arthroscopic intra-articular steroid in combination with morphine and bupivacaine (II-IV).

Relief of post-operative pain is an important part of convalescence following orthopaedic procedures. Inadequate post-operative pain relief can prolong the duration of convalescence, precipitate or increase the duration of hospital stay, increase health care costs, and reduce patient satisfaction. Despite the benefits from effective pain treatment, surveys continue to indicate that acute post-operative pain remains inadequately managed (26).

In pursuit of better post-operative pain control and ease of convalescence and recovery, surgical procedures, such as with arthroscopic surgery, are becoming minimally invasive and conducted in an ambulatory setting with the use of local anaesthetics.

The experience of post-operative pain is subjective and registered in several ways (27-33). In our studies, we used a linear visual analogue scale (VAS). The VAS is

well-validated, reliable, accurate, simple and patient-friendly. The line is 10 cm long with endpoints labelled “no pain” and “worst possible pain”. Following instruction, the patients mark the line at a point corresponding to the intensity of their current pain. The method is valid in young patients but controversial in the elderly (31). We assessed pain on VAS in young patients at rest, during flexion and during walking (I-IV).

3.5. CONVALESCENCE

Convalescence is the time spent recovering from an illness or a treatment. It refers to the later stage when the patient gradually recovers and returns to normal. It includes the period of patient care after surgery during which they are required to attend regular follow-ups. Several factors can extend the duration of convalescence such as pre-operative expectation, post-operative pain and fatigue, lack of appropriate rehabilitation recommendations, social and cultural factors and interposed weekend (7-9, 17, 23-24).

3.6. RECOVERY

Recovery is gained after the end of convalescence. It is restoration or return to any former or better condition. Pain is the main cause of prolonged convalescence and delayed recovery following a variety of ambulatory surgical procedures (34) and major orthopaedic surgery (7-9, 35-37). Patients may return to work even though they may not have recovered. They may still have some pain and reduced function. Recovery has a number of components, one of which is return to work. A number of other measures of recovery, such as pain, reduced motion and strength, or swelling may disappear before return to work or persist after return to work. In our studies, we used return to work as the primary outcome measure of the duration of convalescence (Figure 3.1) (I-IV).

3.7. DESIGN

The dataset included measurement of time until return to work, hours of walking activity, quadriceps strength, range of motion, synovial effusion and use of crutches together with pain profiles. The incentives for accurate reporting were equal in all four studies using a daily questionnaire, thereby allowing linking of the four studies into one dataset. The linking of the datasets provides a more powerful method for

examining new research questions by providing a larger dataset than from a single study.

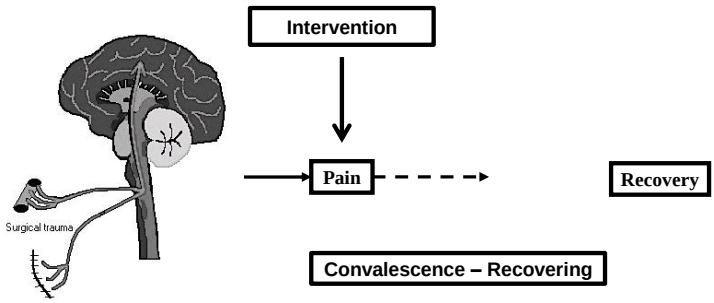

Figure 3.1 Intervention, convalescence and recovery.

Randomisation

The Consolidated Standards of Reporting Trials (CONSORT) statement from 1996, revised in 2001, clearly demonstrate that the randomised clinical trial (RCT) is the superior scientific instrument to assess the validity of results when planning a clinical investigation (38). Even though concealment of group allocation (39) and randomisation are the 'gold standard', these are not always possible with surgical patients (1-3). Randomised trials are the gold standard for determining the efficacy of an intervention. They are internally valid due to design and conduction in order to minimise bias (40-41). To be clinically useful, the results must also be relevant to the clinical setting. This external validity or ability to generalise depends on a representative study sample (40, 42-45). Another problem is the positive effect of being under study, which can affect both the health care staff and the patients in both control and intervention groups, and thereby affect the true result (46).

Sample size calculation

Sample sizes in clinical orthopaedic research are often too small to ensure statistical significance and only 9% of the reviewed RCTs reported a sample size calculation (47). In our RCTs (I-IV), we addressed sample size and power before the initiation of the studies.

A priori, we decided that the clinically relevant difference between control and intervention was the minimal relevant difference of interest (MIREDIFF) to look for in the sample size calculation. Further, we decided that the MIREDIFF should be close or equal to one standard deviation (SD). Since the primary outcome measurements are ordinal and probably normally distributed, we expected that one SD would equal one quartile of the measurements.

Observations on the interval scale and the MIREDIFF formed the basis for calculation of sample size. The type I error (alfa, "α") is when the null hypothesis is rejected given that the null hypothesis is true (α = P (reject H_0 | H_0 is true)). The type II error (beta, "β") is when the null μhypothesis is accepted when the alternative hypothesis is in fact true (β = P (fail to reject the H_0 | H_A is true)). What we want to occur is that we reject the null hypothesis given that the alternative hypothesis is true, given a particular power of the study (power = P (reject H_0 | H_A is true = $1 - \beta$)).

We wanted to be stricter in the first RCT (I) and falsely reject the null hypothesis only 1% of the time ($\alpha = 0.01$). Type I and type II errors were both set at 1% in the first RCT (I), with the risk of increasing the type II error. Therefore, we experienced a longer inclusion period than expected.

Based on the diversity of arthroscopic procedures of the first study, we decided to only include meniscectomy or diagnostic procedures in the following two studies to reduce variability. Subsequently, we decided to reduce sample size and secure power at 80% in the following three RCTs (II-IV). To do this, we kept the difference between the null and alternative hypotheses at 1SD or increased the difference to 1.2 SD. Further, we increased the type I error rate to 5%.

The sample size was calculated using the formula

$$n = n_1 = n_2 = (\sigma^*(z_{1-\alpha/2} + z_{1-\beta})/\delta)^2$$

where MIREDIFF = $\mu_0 - \mu_1 = \delta$, SD = σ, and the statistics $z_{1-\alpha/2}$ and $z_{1-\beta}$ (Figure 3.2).

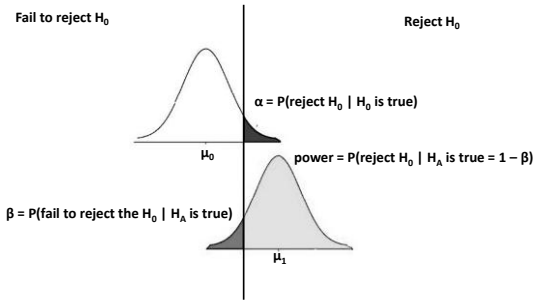

Figure 3.2 Sample size calculation

Validity

Sealed envelopes secured concealment of group allocation. Results were analysed by intention to treat. Two studies used several inclusion criteria (II-III) and one involved two institutions (III). These factors increase the internal validity and lower the external validity of our findings. The two studies complement each other and patients were consecutively enrolled. In the other studies (I, IV), inclusion and exclusion criteria were minimal, thereby increasing the external validity of our findings. We expected our studies to resemble other national and international studies of these cohorts of patients.

Statistics

When calculating sample size, we assume primary outcome measurements probably are normally distributed. Even though the primary outcome measurements look continuous and normally distributed, they are more likely ordered, and the magnitude between steps is uncertain. This makes parametric tests inappropriate since they require assumptions about the underlying distribution of data. This implies the use of non-parametric tests that do not make any or few assumptions about the underlying distribution of data. Data are presented using median and range. We have chosen Wilcoxon Rank Sum Test for independent samples. Where appropriate, we used Chi-square test and ANOVA with mixed model analysis (48). In additional analyses, we used StataIC13 to perform univariate and multivariate regression.

3.8. LITERATURE

The following criteria identified relevant randomised trials:

A. Computer-aided searching of Medline, Scopus, Embase and Cochrane trials register. The search, conducted from 1982 to September 2014, used the combination of the first two levels of the optimal search strategy for randomised trials (49). The search string for pain consisted of “post-operative pain” and “arthroscopy”. The search string for post-operative convalescence consisted of “convalescence” and “arthroscopy”. The search string for recovery was “recovery”, “work”, “sick leave”, “leisure activities” in combination with “arthroscopy”. The search string for intra-articular steroid consisted "Knee", "Knee-Joint", "Arthroscopy", "Adrenal-Cortex-Hormones", "Glucocorticoids Synthetic". The search string for intra-articular pain treatment with morphine and bupivacaine consisted of "Knee", "Knee-Joint", "Arthroscopy", “Intra-articular”, “bupivacaine” and “morphine”.

B. Inspection of reference lists of retrieved reports and review articles.

C. Contact with companies and selected authors in the field to find unpublished studies. D. Use of a personal archive. E. Subject-specific hand searches of the following journals from 1982: Acta Orthopaedica Scandinavia, American and British Journals of Sports Medicine, American and British Journals of Bone and Joint Surgery, and Scandinavian Journal of Medicine and Science in Sports.

Using the inclusion and exclusion criteria, we found eligible trials. Each included trial underwent assessment of methodological quality and data extraction.

CHAPTER 4. SUMMARY OF RESULTS

4.1. THE CLINICAL EFFECT OF NAPROXEN SODIUM AFTER ARTHROSCOPY OF THE KNEE

Figure 4.1 illustrates the flow of patients and table 4.1 presents the characteristics of the patient groups.

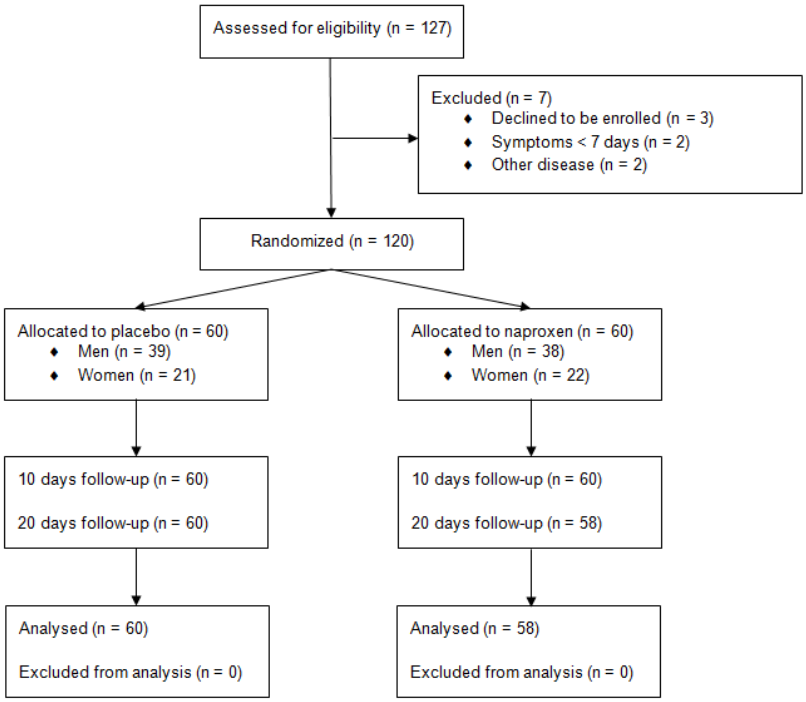

Figure 4.1 Consort flow chart of knee arthroscopy and RCT of oral naproxen versus placebo.

Of the 127 patients assessed, 120 were eligible. Two patients in the naproxen group were lost to follow up.

The trial revealed a decrease in the time to return to work by the use of naproxen compared to placebo during the 20 days of follow-up. The time to return to work was 14 (10-31) days for naproxen compared to 17 (11-31) days for placebo ($P < 0.0001$ (Figure 4.2)). There was a difference in walking activity the first 10 days ($P = 0.01$), in use of crutches ($P = 0.01$, days until pain-free ($P = 0.0001$), range of

motion (ROM) (P = 0.01), synovial effusion (P = 0.01) and quadriceps strength (P = 0.04).

	Placebo	Naproxen
Sex M/F	38/22	39/21
Age	35 (18-64)	34 (18-65)
Medial meniscal lesion	29	24
Lateral meniscal lesion	11	9
Chondromalacia	22	15
Cartilage lesion	22	20
Ant. cruciate ligament rupture	7	8
No pathology	5	8
No surgery	11	18
Operation time (min.)	30 (10-75)	30 (15-80)

Table 4.1 Demographic data in patients undergoing knee arthroscopy and RCT of oral naproxen versus placebo (median and range) (Rasmussen 1993 (I)).

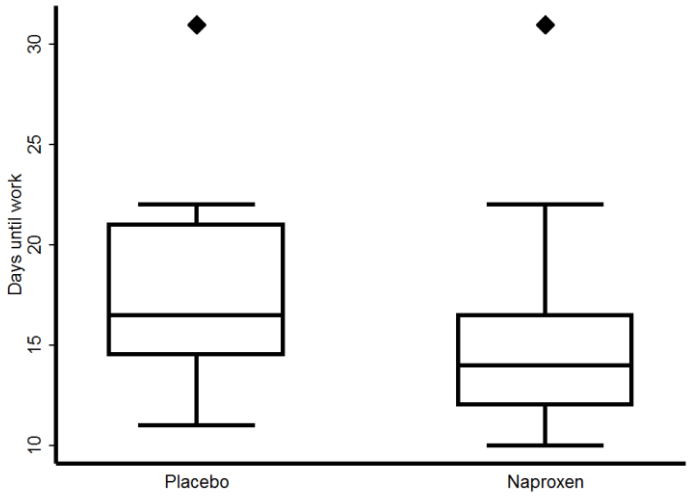

Figure 4.2 Box and whisker graph of the dependent variable days until return to work after knee arthroscopy for the independent variables naproxen and placebo (minimum, first quartile, median, third quartile and maximum) (P < 0.0001).

There was a difference in pain across the repeated measurements at 12 time points after knee arthroscopy (Figure 4.3) (P = 0.004). The measurement of pain was not specified in relation to rest or activity.

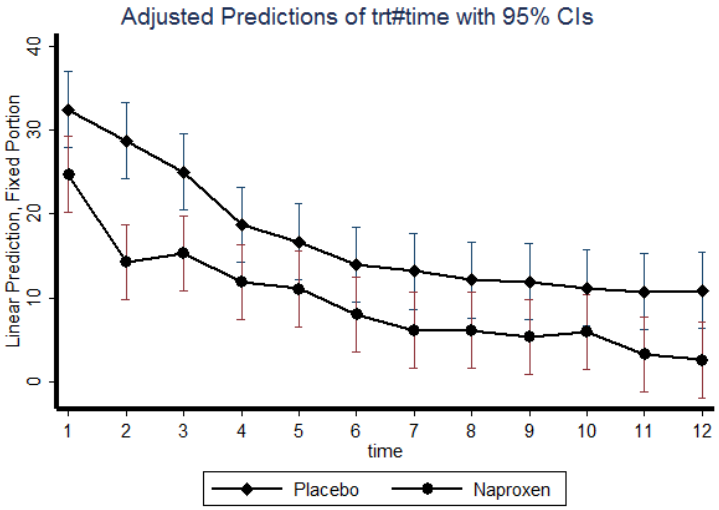

Figure 4.3 Pain (mean and 95% confidence interval) at 12 time points during 10 days after knee arthroscopy.

4.2. INTRA-ARTICULAR GLUCOCORTICOID, BUPIVACAINE AND MORPHINE REDUCES PAIN, INFLAMMATORY RESPONSE AND DURATION OF CONVALESCENCE AFTER ARTHROSCOPIC MENISCECTOMY

Figure 4.4 illustrates the flow of patients and table 4.2 presents the characteristics of the patient groups.

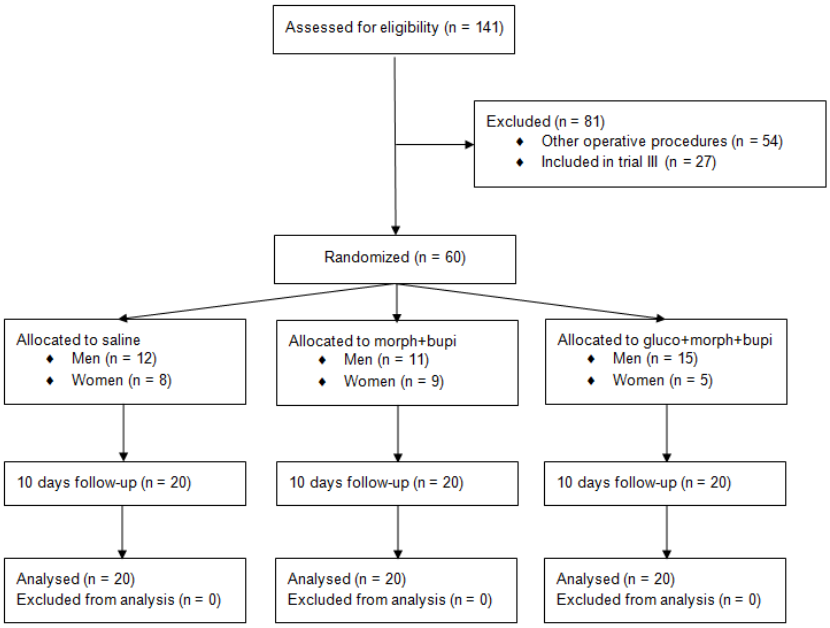

Figure 4.4 Consort flow chart of arthroscopic meniscectomy and RCT of intra-articular saline, morphine+bupivacaine or glucocorticoid+morphine+bupivacaine.

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Of the 141 patients assessed, 60 were eligible. None of the patients were lost to follow up.

The trial revealed a reduction in the time to return to work by the use of methylprednisolone and bupivacaine plus morphine during the 10 days of follow-up. The time taken to return to work was 3 (0-13) days for methylprednisolone + morphine + bupivacaine compared to 5 (1-14) for morphine + bupivacaine and for placebo, 10 (1-30) days (Figure 4.5) ($P < 0.0001$).

	S	B+M	B+M+MP
Sex M/F	12/8	11/9	15/5
Age	40 (18-61)	40 (18-55)	39 (18-55)
Medial meniscal lesion	17	16	17
Lateral meniscal lesion	3	4	3
Longitudinal lesion	16	17	18
Radial lesion	4	3	2
Operation time (min.)	30 (15-60)	30 (15-75)	30 (15-70)

Table 4.2 Demographic data in patients undergoing arthroscopic meniscectomy and RCT of intra-articular saline (S), bupivacaine and morphine (B+M) or bupivacaine, morphine and methylprednisolone (B+M+MP). (median and range) (Rasmussen 1998 (II)).

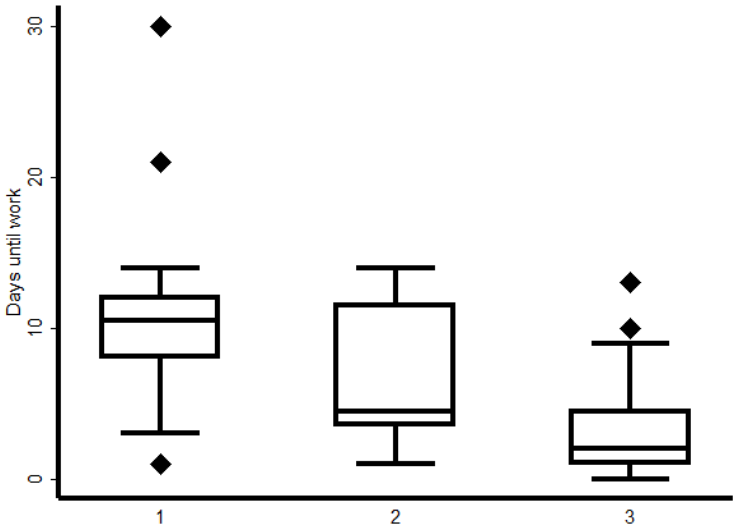

Figure 4.5 Box and whisker graph of the dependent variable days until return to work after arthroscopic knee meniscectomy for the independent variables placebo "1", morphine plus bupivacaine "2" and methylprednisolone plus morphine plus bupivacaine "3" (minimum, first quartile, median, third quartile and maximum). There was a difference between the groups ($P < 0.0001$).

There was a difference in hours of walking activity (P = 0.001), use of crutches (P = 0.0001), days until pain-free (P < 0.0001), range of motion (P = 0.004), synovial effusion (P = 0.007) and quadriceps strength (P = 0.0001)

There was a difference in pain across the repeated measurements at 14 time points after arthroscopic knee meniscectomy (Figure 4.6) (P = 0.0001). The measurement of pain was performed at 90 degrees of knee flexion.

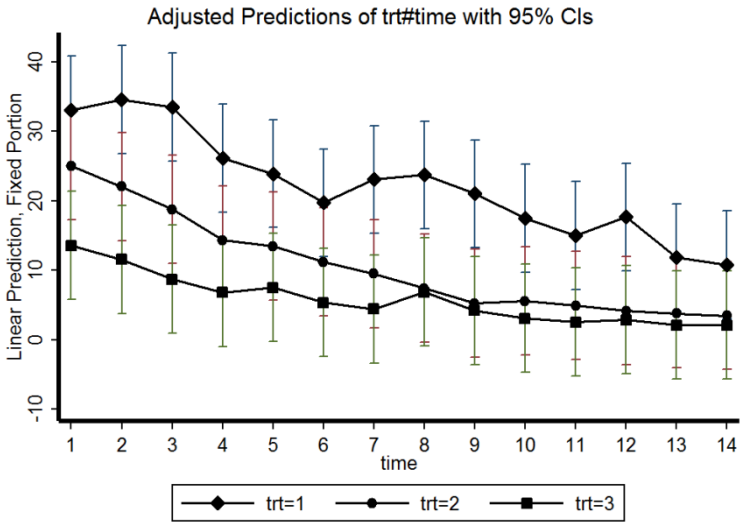

Figure 4.6 Pain (mean and 95% confidence interval) at 90 degrees of flexion at 14 time points during 10 days after arthroscopic knee meniscectomy. There was a difference between placebo (trt=1), morphine + bupivacaine (trt=2) and methylprednisolone + morphine + bupivacaine (trt=3) (P = 0.001).

4.3. COMBINED INTRA-ARTICULAR GLUCOCORTICOID, BUPIVACAINE AND MORPHINE REDUCES PAIN AND THE DURATION OF CONVALESCENCE AFTER DIAGNOSTIC KNEE ARTHROSCOPY

Figure 4.7 illustrates the flow of patients and table 4.3 presents the characteristics of the patient groups.

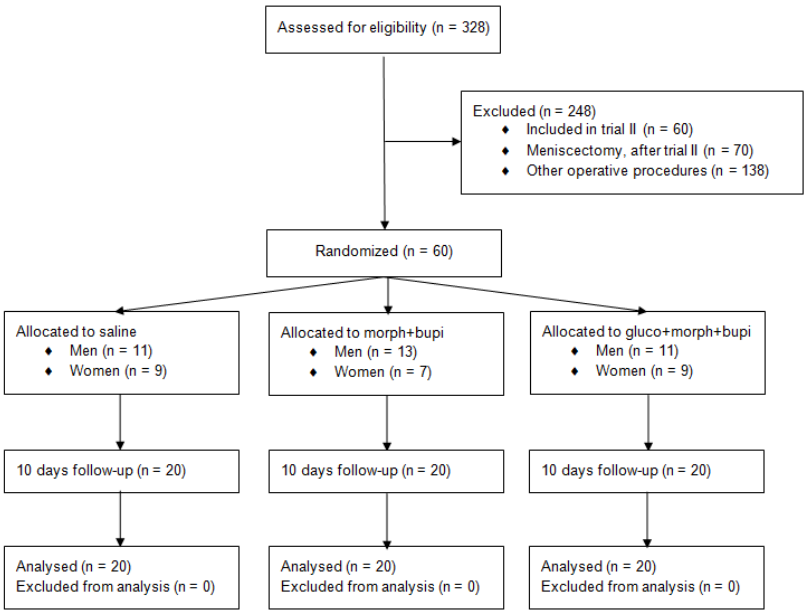

Figure 4.7 Consort flow chart of diagnostic arthroscopy and RCT of intra-articular saline, morphine+bupivacaine or glucocorticoid+morphine+bupivacaine.

Of the 328 patients assessed, 60 were eligible. None of the patients were lost to follow up.

The trial revealed a reduction in the time to return to work by the use of methylprednisolone and bupivacaine plus morphine during the 10 days of follow-up. The time taken to return to work was 2 (0-15) days for methylprednisolone + morphine + bupivacaine compared to 5 (1-10) days for morphine + bupivacaine and 10 (1-14) days for placebo (Figure 4.8) ($P < 0.0001$). There was a difference in hours of walking activity ($P = 0.005$), use of crutches ($P < 0.0001$), days until pain-free ($P < 0.0001$), range of motion ($P = 0.06$), synovial effusion ($P < 0.0001$), quadriceps strength ($P < 0.0001$)

	S	B+M	B+M+MP
Sex M/F	11/9	13/7	11/9
Age	32 (21-54)	26 (19-53)	29 (18-52)
Normal	7	8	7
Osteoarthritis	5	7	6
Chondromalacia patellae	3	2	2
Cartilage lesion	2		2
Osteochondritis	1	2	1
Anterior cruciate ligament rupture	2	1	2
Operation time (min.)	20 (10-45)	25 (15-45)	20 (15-45)

Table 4.3 Demographic data of patients undergoing diagnostic arthroscopy and RCT of intra-articular saline (S), bupivacaine and morphine (B+M) or bupivacaine, morphine and methylprednisolone (B+M+MP) (median and range). (Rasmussen 2002 (III)).

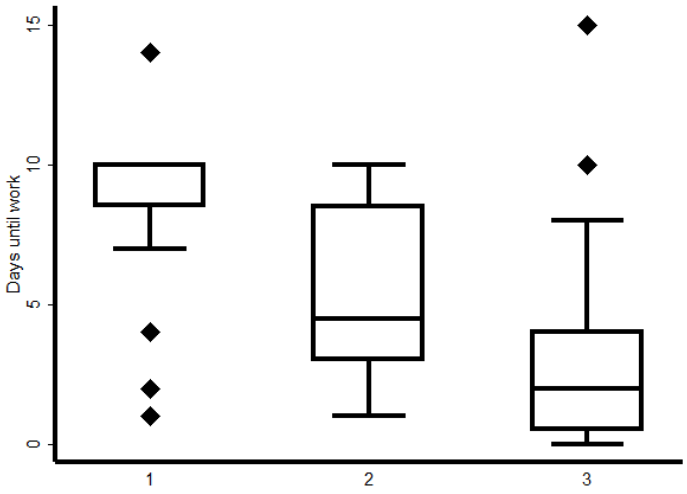

Figure 4.8 Box and whisker graph of the dependent variable days until return to work after diagnostic knee arthroscopy for the independent variables placebo "1", morphine plus bupivacaine "2" and methylprednisolone plus morphine plus bupivacaine "3" (minimum, first quartile, median, third quartile and maximum). There was a difference between the groups ($P < 0.001$).

There was a difference in pain across repeated measurements at 14 time points after diagnostic knee arthroscopy (Figure 4.9) ($P < 0.0001$). The measurement of pain was performed at 90 degrees of knee flexion.

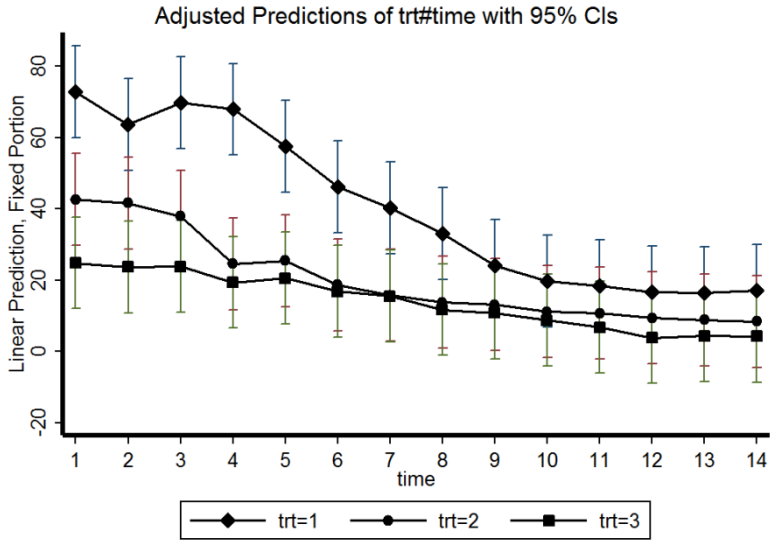

Figure 4.9 Pain (mean and 95% confidence interval) at 90 degrees of flexion at 14 time points during 10 days after diagnostic knee arthroscopy. There was a difference between placebo (trt=1), morphine + bupivacaine (trt=2) and methylprednisolone + morphine + bupivacaine (trt=3) ($P < 0.0001$).

4.4. INTRA-ARTICULAR GLUCOCORTICOID, BUPIVACAINE AND MORPHINE REDUCES PAIN AND THE DURATION OF CONVALESCENCE AFTER ARTHROSCOPIC ANKLE SURGERY

Figure 4.10 illustrates the flow of patients and Table 4.4 presents the characteristics of the patient groups.

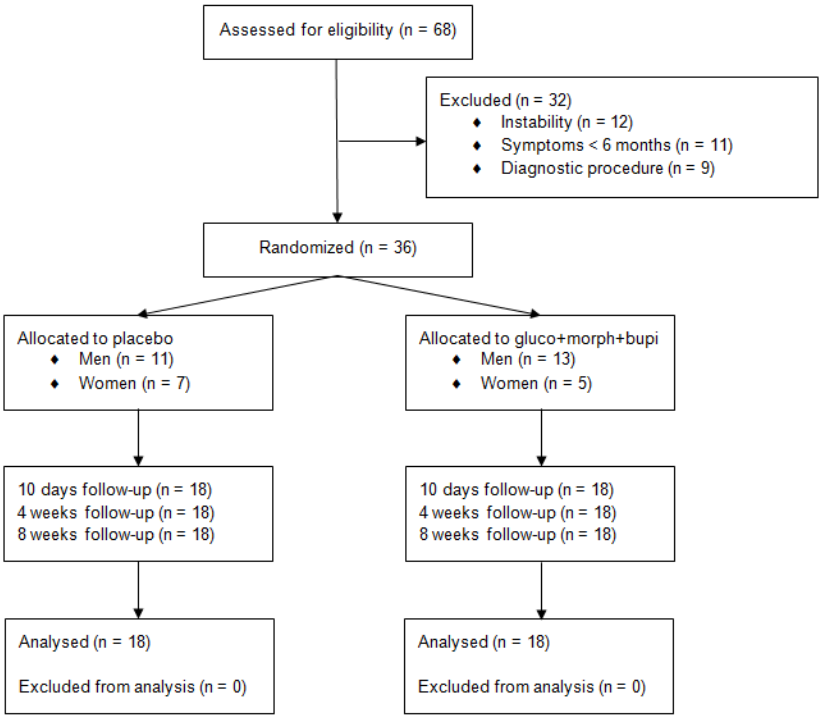

Figure 4.10 Consort flow chart of ankle arthroscopy and RCT of intra-articular saline or glucocorticoid+morphine+bupivacaine.

Of the 68 patients assessed, 36 were eligible. None of the patients were lost to follow up.

The trial revealed a reduction in the time to return to work by the use of methylprednisolone and bupivacaine plus morphine during the 10 days of follow-up. The time taken to return to work was 2 (1-21) days for methylprednisolone + morphine + bupivacaine compared to 7 (1-52) days for placebo (Figure 4.11) (P = 0.016).

	Saline	B+M+MP
Sex M/F	11/7	13/5
Age	32 (24-50)	33 (19-52)
Synovitis	18	18
Bony Spurs	18	18
Loose body	3	2
Cartilage lesion	3	4
Operation time (min.)	45 (30-70)	45 (25-65)

Table 4.4 Demographic data in patients undergoing ankle arthroscopy and RCT of intra-articular saline or glucocorticoid+morphine+bupivacaine (median and range). (Rasmussen 2000 (IV))

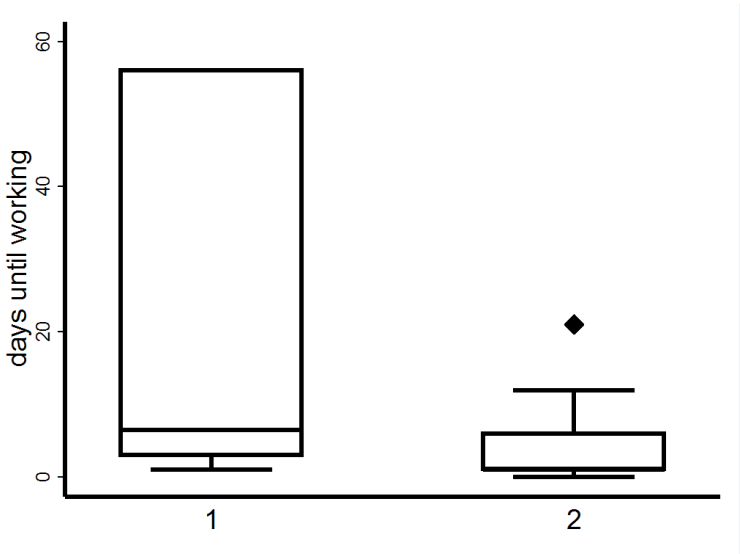

Figure 4.11 Box and whisker graph of the dependent days until return to work after ankle arthroscopy for the independent variables placebo "1" and methylprednisolone+ morphine+bupivacaine "2". (P = 0.016).

There was a difference in hours of walking activity (P = 0.024), use of crutches (P < 0.0001), days until pain-free (P < 0.0001), and synovial effusion (P = 0.003) but not in range of motion (P = 0.65).

There was a difference in pain across repeated measurements at 14 time points after operative ankle arthroscopy (Figure 4.12) (P = 0.04). The measurement of pain was performed when walking.

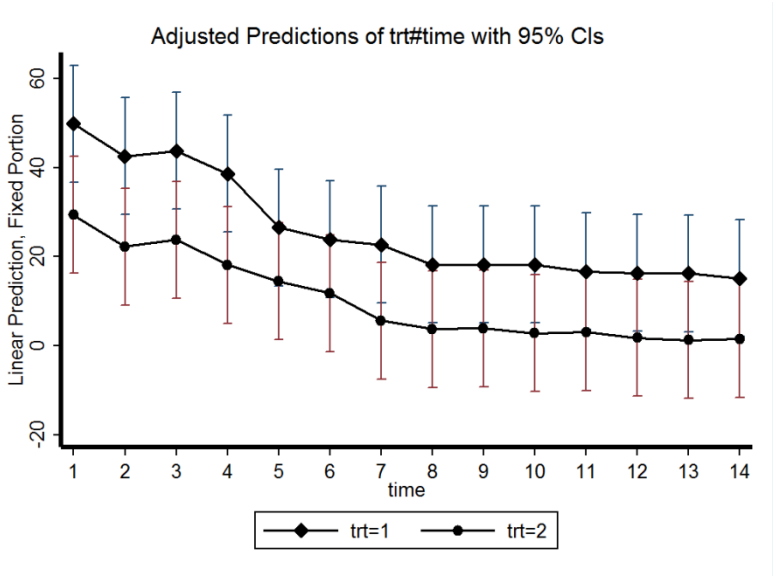

Figure 4.12 Pain (mean and 95% confidence interval) walking at 14 time points during 10 days after operative ankle arthroscopy. There was a difference between placebo (trt=1) and methylprednisolone + morphine + bupivacaine (trt=2) (P = 0.041).

CHAPTER 5. ADDITIONAL ANALYSIS

5.1. NAPROXEN SODIUM AFTER KNEE ARTHROSCOPY

There was a variation in the results depending on the type of surgery when analysing the data from trial I. Based on this observation, we had two independent predictor variables, "naproxen or placebo" and "operative or diagnostic arthroscopy". To investigate the effect of naproxen sodium after operative arthroscopy, we performed a univariate regression and a multivariate multiple regression analysis of the data at 10 days follow-up (Table 5.1 and 5.2). The multivariate multiple regression investigated the dependent variables (time to return to work, walking, use of crutches, days until pain-free, range of motion, synovial effusion and strength) to be predicted from Naproxen or placebo and operative or diagnostic arthroscopy. When adjusting for operative arthroscopy, there was still an effect of naproxen sodium on recovery (Table 5.2).

		t	P	Coef (95 % CI)
Naproxen				
	Work, days	-3.97	<0.0001	-3.08 (-4.62 – -1.55)
	Walking, hours	2.14	0.035	12.5 (0.03 – 24.1)
	Crutches, days	-2.35	0.021	-1.49 (-2.74 – -0.23)
	Pain free, days	-3.46	0.001	-2.68 (-4.22 - -1.15)
	ROM, degree	2.52	0.013	13.7 (2.95 – 24.5)
	Effusion, yes/no, 1/0	-1.92	0.058	-0.17 (-0.34 – -0.0056)
	Strength, normal/reduced	1.88	0.063	0.17 (-0.0091 – 0.34)
Operative arthroscopy				
	Work, days	-0.16	0.846	-0.16 (-2.17 – 1.86)
	Walking, hours	-1.99	0.049	-14.1 (-28.2 – -0.07)
	Crutches, days	1.30	0.197	1.02 (-0.54 – 2.57)
	Pain free, days	-0.55	0.58	-0.55 (-2.52 – 1.42)
	ROM, degree	-2.93	0.004	-19.3 (-32.4 – -6.23)
	Effusion, yes/no, 1/0	3.56	0.001	0.37 (0.16 – 0.58)
	Strength, normal/reduced	-2.45	0.016	-0.26 (-0.47 – -0.05)

Table 5.1 Univariate regression analysis of data at 10 days follow-up after knee arthroscopy of 120 patients.

	t	P	Coef (95% CI)
Return to work, days			
Naproxen	-3.68	<0.0001	-2.96 (-4.55 – -1.37)
Operative arthroscopy	-0.25	0.801	-0.25 (-2.17 – 1.68)
Walking, hours			
Naproxen	2.72	0.008	15.7 (4.25 – 27.1)
Operative arthroscopy	-1.92	0.058	-13.4 (-27.2 – 0.45)
Crutches, days			
Naproxen	-1.94	0.055	-1.24 (-2.51 – 0.024)
Operative arthroscopy	1.39	0.166	1.08 (-0.45 – 2.61)
Days until pain free			
Naproxen	-3.59	0.001	-2.84 (-4.41 – 1.27)
Operative arthroscopy	-0.72	0.475	-0.67 (-2.58 – 1.21)
ROM, degree			
Naproxen	2.55	0.012	13.6 (3.03 – 24.3)
Operative arthroscopy	-2.70	0.008	-17.5 (-30.3 – -4.66)
Effusion, yes/no, 1/0			
Naproxen	-1.81	0.074	-0.15 (-0.33 – 0.015)
Operative arthroscopy	3.65	0.000	0.38 (0.17 – 0.59)
Strength, normal/reduced, 1/0			
Naproxen	1.84	0.068	0.16 (0.012 – 0.33)
Operative arthroscopy	-2.39	0.018	-0.25 (-0.46 – -0.041)

Table 5.2 Multivariate multiple regression of data at 10 days follow-up after knee arthroscopy of 120 patients.

5.2. INTRA-ARTICULAR PAIN TREATMENT AFTER KNEE ARTHROSCOPY

Two studies (II-III) of intra-articular treatment included arthroscopic knee meniscectomy and diagnostic knee arthroscopy. When analysing the results of the two studies separately, we found a variation indicating that intra-articular treatment is less efficient after meniscectomy. To investigate whether the combined intra-articular treatment reduces the duration of convalescence, we linked the data from these two studies and performed a univariate and a multivariate multiple regression analysis at 10 days follow-up (Tables 5.3 and 5.4).

Adjusting for the surgical procedure, there was a positive effect of the combination of bupivacaine plus morphine plus methylprednisolone on all parameters ($P < 0.0001$) (Table 5.4).

		t	P	Coef (95% CI)
Intraarticular treatment				
	Return to work, days	-6.8	<0.0001	-2.24 (-4.18 – -2.3)
	Walking, hours	5.47	<0.0001	21.5 (14 – 29)
	Crutches, days	-6.18	<0.0001	-1.9 (-2.5 – -1.3)
	Pain free, days	-8.15	<0.0001	-2.86 (-3.56 – -2.16)
	ROM, degree	3.83	<0.0001	6.44 (3.11 – 9.8)
	Effusion, yes/no, 1/0	-4.82	<0.0001	-0.25 (-0.35 – -0.14)
	Strength, normal/reduced	6.69	0.002	0.32 (0.23 – 0.42)
Meniscectomy				
	Return to work, days	1.43	0.155	1.3 (-0.5 – 3.1)
	Walking, hours	1.02	0.311	7.7 (-7.3 – 22.6)
	Crutches, days	-2.98	0.004	-1.66 (-2.77 – -0.56)
	Pain free, days	-0.12	0.91	-0.83 (-1.5 – 1.33)
	ROM, degree	-0.31	0.75	-0.91 (-6.7 – 4.8)
	Effusion, yes/no, 1/0	1.0	0.318	0.09 (-0.88 – 0.27)
	Strength, normal/reduced	-1.94	0.055	-0.17 (-0.36 – 0.004)

Table 5.3 Univariate regression analysis of data at 10 days follow-up after knee arthroscopy of 120 patients.

		t	P	Coef (95% CI)
Return to work, days				
	Intraarticular treatment	-5.79	<0.0001	-3.04 (-4.1 – 2)
	Meniscectomy	0.84	0.4	0.74 (-1 – 2.5)
Walking hours				
	Intraarticular treatment	5.1	<0.0001	20.6 (12.6 – 28.6)
	Meniscectomy	0.88	0.383	5.9 (-7.5 – 19.4)
Crutches, days				
	Intraarticular treatment	-5.52	<0.0001	-1.8 (-2.4 – -1.13)
	Meniscectomy	-3.48	0.001	-1.9 (-2.9 – -0.8)
Pain free, days				
	Intraarticular treatment	-6.74	<0.0001	-2.5 (-3.3 – -1.8)
	Meniscectomy	-1.42	0.159	-0.89 (-2.14 – 0.36)
ROM, degree				
	Intraarticular treatment	3.67	<0.0001	6.84 (3.14 – 10.5)
	Meniscectomy	-0.39	0.699	-1.22 (-7.44 – 5)
Effusion, yes/no, 1/0				
	Intraarticular treatment	-4.51	<0.0001	-0.24 (-0.35 – -0.14)
	Meniscectomy	0.72	0.47	0.07 (-0.11 – 0.25)
Strength, normal/reduced, 1/0				
	Intraarticular treatment	6.73	<0.0001	0.33 (0.23 – 0.43)
	Meniscectomy	-2.45	0.016	-0.2 (-0.37 – -0.04)

Table 5.4 Multivariate multiple regression of data at 10 days follow-up after knee arthroscopy of 120 patients

5.3. USE OF TOURNIQUET IN KNEE ARTHROSCOPY

In the study of NSAIDs after knee arthroscopy, we used a tourniquet to achieve a bloodless field (I). The two studies of intra-articular treatment after knee arthroscopy did not use a tourniquet (II-III). In the NSAIDs study, the median number of days for return to work was 16 (I), and for the linked study of intra-articular treatment, 5 days (II-III). There was a difference in the time to return to work between use of a tourniquet or not with ($P < 0.0001$). In diagnostic knee arthroscopy, there was a difference ($P < 0.0001$), and in operative arthroscopy, there was a difference ($P < 0.0001$) (Figure 5.1).

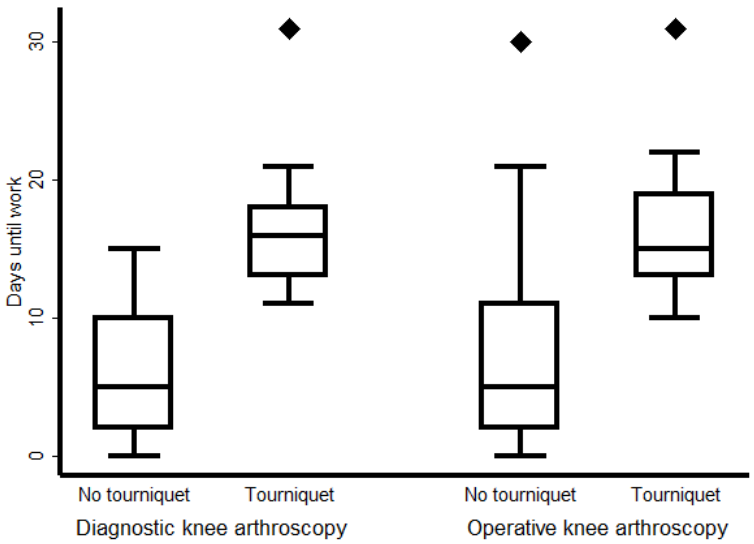

Figure 5.1 Box and whisker graph of the dependent days until work after knee arthroscopy for the independent variables tourniquet use and operative procedure of 240 patients. Diagnostic knee arthroscopy ($P < 0.0001$) and operative knee arthroscopy ($P < 0.0001$).

A possible confounder may be the use of intra-articular treatment in study II and III and no use of post-operative NSAIDs in study I. Excluding intra-articular treatment and no post-operative NSAIDs, there was a difference in return to work between the use of a tourniquet or not with ($P < 0.0001$). For diagnostic knee arthroscopy, there was a difference ($P < 0.0001$) and for operative arthroscopy, there was a difference ($P = 0.0001$) (Figure 5.2).

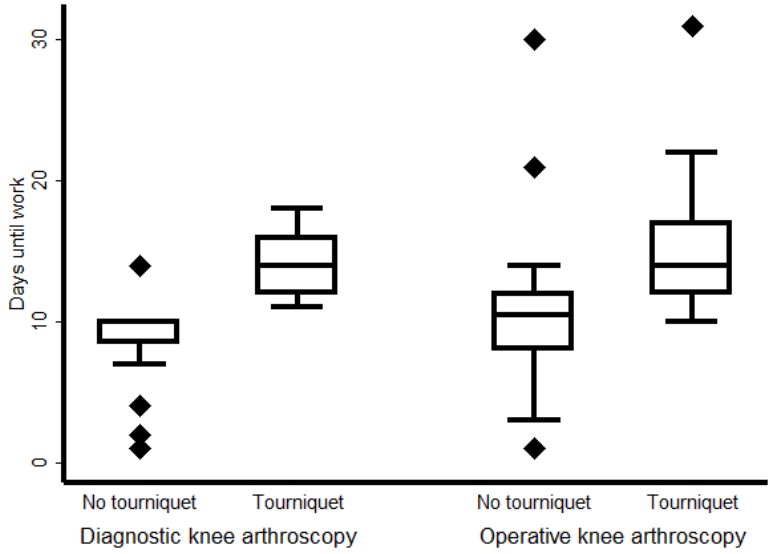

Figure 5.2 Box and whisker graph of the dependent time to return to work after knee arthroscopy for the independent variables tourniquet use and operative procedure of 100 patients receiving oral NSAIDs and no intra-articular treatment. Diagnostic knee arthroscopy ($P < 0.0001$) and operative knee arthroscopy ($P = 0.0001$).

We found a variation in the results depending on the type of surgery and the use of a tourniquet or not. Based on this observation we had two independent predictor variables, "tourniquet" and "operative or diagnostic arthroscopy". To investigate this, we performed a multivariate multiple regression analysis of the data at 10 days follow-up (Table 5.5). In the analysis are included 60 patients from the NSAIDs study (I), and 40 patients from the studies of intra-articular treatment who received post-operative NSAIDs and no intra-articular treatment (II-III).

The analysis shows a statistically significant difference with/without tourniquet use on days until return to work, pain, range of motion, synovial effusion and quadriceps strength. The estimated effect of tourniquet use on the duration of convalescence was 4.88 (3.01 – 6.75) days.

	t	P	Coef (95% CI)
Return to work, days			
Tourniquet	5.19	<0.0001	4.88 (3.01 – 6.75)
Operative arthroscopy	1.47	0.144	1.4 (-0.49 – 3.33)
Walking, hours			
Tourniquet	1.36	0.178	9.1 (-4.2 – 22.4)
Operative arthroscopy	-0.61	0.545	4.16 (-17.8 – 9.43)
Crutches, days			
Tourniquet	-0.80	0.424	0.62 (-2.15 – 0.91)
Operative arthroscopy	-0.90	0.373	-0.7 (-2.26 – 0.86)
Days until pain free			
Tourniquet	6.68	<0.0001	4.88 (3.43 – 6.38)
Operative arthroscopy	0.30	0.763	0.23 (-2.26 – 0.86)
ROM, degree			
Tourniquet	-2.40	0.0018	-13 (-24 – -2.25)
Operative arthroscopy	-0.30	0.763	-1.67 (-12.6 – 9.27)
Effusion, yes/no, 1/0			
Tourniquet	4.21	<0.0001	0.42 (0.22 - 0.63)
Operative arthroscopy	-1.38	0.171	0.14 (-0.35 – 0.063)
Strength, normal/reduced, 1/0			
Tourniquet	- 6.77	<0.0001	-0.61 (-0.79 – -0.43)
Operative arthroscopy	2.03	0.045	-0.19 (-0.004 – -0.37)

Table 5.5 The effect of tourniquet use on recovery. Multivariate multiple regression of 100 patients receiving oral NSAIDs and no intra-articular treatment.

CHAPTER 6. DISCUSSION

6.1. MAIN FINDINGS

The results of the four studies (I-IV) indicate that post-operative use of oral NSAIDs and intra-articular multimodal pain treatment result in a faster recovery. The use of a tourniquet and the impact of surgical procedures hamper the effect of pain treatment on recovery.

NSAIDs after knee arthroscopy

Post-operative use of NSAIDs has a clinical effect on recovery after knee arthroscopy (I). There was an effect on time to return to work, hours of walking activity the first 10 days, use of crutches, days until pain-free, and range of motion. The effect was to some degree counteracted by the impact of the surgical procedure when measuring synovial effusion and quadriceps strength. In operative arthroscopy, there was a benefit of NSAIDs on effusion and quadriceps strength, but not in diagnostic arthroscopy. The improvement in muscular strength after operative arthroscopy may be due to both a reduction in effusion and the analgesic effect. The lack of improvement after diagnostic arthroscopy may be due to the surgical procedure being minor and the ensuing effusion and pain being minimal. Repeated measurement of pain during the first 10 post-operative days found an effect of treatment with NSAIDs to some degree but it did not persist. This was probably due to the measurement of pain not being specific in relation to rest or activity.

Intra-articular analgesia after meniscectomy

Intra-articular injection of methylprednisolone after arthroscopic knee meniscectomy had a clinical effect on recovery (II). There was an effect on time to return to work, use of crutches, hours of walking activity within the first 10 days, days until pain-free and range of motion. Morphine plus bupivacaine evaluated against placebo had a similar effect on recovery. In repeated measurement of pain between the three groups, there was an effect on pain at 90 degrees of flexion on pain during leg lift and stair walking.

Intra-articular analgesia after diagnostic knee arthroscopy

After diagnostic knee arthroscopy, intra-articular injection of methylprednisolone had a clinical effect on recovery (III). There was an effect on time to return to work, hours of walking within the first 10 days, days with crutches, days until pain-free and synovial effusion. Morphine plus bupivacaine evaluated against placebo had a similar effect on recovery. In repeated measurement of pain between the three groups, there was an effect on pain at 90 degrees of flexion, during leg lift and stair walking.

Intra-articular analgesia after operative ankle arthroscopy

In operative ankle arthroscopy, there was a beneficial effect of multimodal intra-articular treatment on recovery (IV). There was an effect on days until return to work, hours of walking activity within the first 10 days, use of crutches, days until pain-free and synovial effusion. There was an effect on repeated measurements of pain when walking.

NSAIDs after operative knee arthroscopy

An additional multivariate multiple regression analysis revealed the major counteracting effect of operative arthroscopy against the effect of NSAIDs on recovery (Table 5.1 and 5.2). The analysis proved the impact of surgical trauma and the necessity to distinguish between operative and diagnostic knee arthroscopy in future trials. Further, the analysis proved the limited efficacy of NSAIDs alone on recovery.

Intra-articular analgesia after knee arthroscopy

Two studies investigated the effect of intra-articular methylprednisolone, morphine and bupivacaine after arthroscopic knee meniscectomy and diagnostic knee arthroscopy (II-III). As in the previous study (I), when evaluating the results, the multimodal treatment seems more effective after diagnostic arthroscopy than after arthroscopic meniscectomy. The ANOVA analysis, especially, reveals a better effect of treatment over time after diagnostic than after arthroscopic knee meniscectomy. Again, the impact or size of the surgical trauma seems to counteract the effect of the multimodal intra-articular treatment, especially methylprednisolone. An additional multivariate multiple regression analysis proved

the effect of intra-articular treatment on recovery and revealed a minor counteracting effect of meniscectomy (Tables 5.3 and 5.4).

Use of a tourniquet

Pooling all data from the three studies showed that there was a clinical effect of tourniquet use on days until return to work (Figure 5.1). Excluding both intra-articular treatment and no post-operative NSAIDs, the effect of a tourniquet was consistent. An additional multivariate multiple regression analysis of this subgroup proved the effect of tourniquet use on recovery (Table 5.5). There was an effect of tourniquet use on pain, range of motion, effusion and muscle strength.

6.2. MONITORING SHORT-TERM POST ARTHROSCOPIC RECOVERY

We used days until return to work, hours of walking activity, use of crutches, and days until pain-free to monitor the patient-reported recovery. Days to return to work was the primary outcome measure. For the physical examination at follow-up, we used range of motion, effusion and muscular strength to monitor signs of recovery.

The patient-reported recovery measures reflect what matters to the patients rather than to the physicians. Moreover, the measures used carefully worded language that the patients use. The questionnaire was easily accepted and completed. Further, the selected measures evaluated independent physical recovery.

The goals after arthroscopy are several, with a focus on return to work and normal activity (50). One is to restore range of motion to the same degree as that of the unaffected side in order to restore biomechanical alignment and function. Another goal is to restore muscular strength to ensure biomechanical support of the joint. Yet another is to restore gait to prevent disuse of the quadriceps. Full pain-free activity is important to prevent contracture and arthrofibrosis. In 2001, O`Connor (50) stated that range of motion, quadriceps strength and gait are the most important measures of post-operative recovery. In a recent review (15) of the effectiveness of post-operative physiotherapy after arthroscopic knee meniscectomy, the most important measures of recovery in 18 placebo-controlled randomised trials were days to return to work (2 trials), range of motion (8 trials), quadriceps strength (10 trials), effusion (4 trials), activity pain (2 trials) and gait (1 trial).

The primary outcome and convalescence measure, days to return to work, was easy to monitor. This measure in our studies (I-IV) revealed clinically significant evidence of the efficacy of multimodal intra-articular treatment. Days to return to work also reflects the effectiveness of arthroscopy and may form the basis for cost-benefit analysis.

Hours of walking activity during the first 10 days after arthroscopy had a wide range from < 10 hours (I-II) to 189 hours (IV). This may indicate a reporting bias. In diagnostic knee arthroscopy (III) there was a tendency towards a non-significant increase in walking activity in the placebo group compared to that of the morphine plus bupivacaine group. The measure of hours of walking activity did not reveal any effect of tourniquet use or operative arthroscopy in subgroup analysis.

Use of crutches the first 10 days after arthroscopy ranged from 0 to 10 in all of the four studies. The measure of use of crutches did not reveal any effect of tourniquet use or operative arthroscopy in subgroup analysis.

Days until pain-free after the arthroscopy was easily monitored and revealed significance in all analyses.

Range of motion at 10 days follow-up was easy to monitor even though the range was between 25 and 150 degrees (I) and between 75 and 160 degrees (II-III). The measure did not reveal significance in ankle arthroscopy. The measure did reveal significance in the other analyses.

Effusion, measured as yes or no was statistically significant in all analyses. However, when quantified in this way, it is not easily monitored.

Quadriceps strength classified as normal or reduced revealed significance in all analyses. However, when quantified in this way, it is also not easily monitored.

In monitoring short-term recovery after arthroscopy, days to return to work seems to be the most efficient and use of crutches less efficient. According to the multivariate multiple regression analysis (Tables 3, 5 and 6), all but use of crutches seems to be useful in monitoring short-term recovery after arthroscopy.

Days to return to work and time until pain-free seem to be the most important in evaluating the effectiveness of pain treatment after knee and ankle arthroscopy.

6.3. INTERPRETATION OF THE RESULTS AND COMPARISON WITH THE LITERATURE

NSAIDs – efficacy and results

Knee arthroscopy is a common procedure that has been routinely performed on an outpatient basis for more than two decades. Arthroscopy has spared the patients large incisions and decreased their morbidity, but not eliminated their pain. The internal surgical site, including the synovial tissue, the anterior fat pad and the joint capsule have free nerve endings that are capable of sensing painful stimuli and producing pain (51-53).

The surgical trauma promotes expression of cyclooxygenase in both the peripheral nervous system and the central nervous system, leading to an increase in the release of prostaglandins, induction of pain and localised hyperalgesia and hypersensitivity. Therefore, inhibition of the prostaglandin release may be effective in preventing the development of pain after arthroscopy. The use of NSAIDs is common in the treatment of inflammation and pain resulting from rheumatic disease, sports and other injuries and less common in postoperative pain management.

In outpatient surgery, effective pain relief is demanded and especially to allow early mobilisation. In the multimodal analgesic approach, there is still no consensus today as to the use of NSAIDs. There are limited guidelines concerning the peroral postoperative pain management after knee arthroscopy. The management varies from paracetamol only to combinations with codeine and morphine. The use of NSAIDs is in addition or as an alternative. In major surgery, there is an opioid sparing effect of NSAIDs and a shortening of hospital stay (23, 25, 54-56) but the benefit in terms of reduction in morphine-related adverse effects seems not to favour their use.

Knee arthroscopy is associated with pain, swelling and discomfort requiring medication for several days after surgery (57-58). Swelling and discomfort further delay rehabilitation for up to 2 weeks after surgery (57-58). NSAIDs exert an opioid sparing effect in the post-operative period (59). That is particularly helpful in ambulatory surgical patients, in whom pain and nausea are common causes of delayed discharge (60). Further, patients unable to complete a rehabilitation program may be at increased risk of developing post-operative complications such as delay in strength recovery, prolonged knee stiffness and anterior knee pain (57-58, 61).

In a prospective study, we investigated the effects of 10 days of treatment with NSAIDs after arthroscopic surgery (I). Patients reported days to return to work, pain, use of crutches and hours of activity for 20 days. At the 10-day and 20-day follow-ups, we measured synovial effusion, range of movement and quadriceps

strength. When performing meniscectomy or other arthroscopic procedures, there was a significant effect of NSAID whereas after diagnostic arthroscopy, the effects of NSAIDs was minimal. This indicates that the benefits of NSAIDs relate to the severity of, and the reduction of the inflammatory response to, the surgical trauma. Further, the study demonstrates the primary outcome measures for evaluating modulation of the stress response are time to return to work and degree of activity.

NSAIDs – literature review

A methodological search in September 2014 found 33 studies for other randomised controlled trials of NSAIDs after arthroscopic knee surgery (16, 62-95). Most of the trials have investigated the effects of NSAIDS on pain measured on VAS and the use of other analgesics. Unfortunately, the trials had poor or moderate methodological quality. They used inadequately defined measures of post-operative pain not related to the inflammatory response, function or activity. Five studies compared different NSAIDs treatment (69, 73, 75, 77, 80) whereas 28 compared NSAIDs to other analgesics or placebo. Three studies only investigated bleeding and coagulation showing little or no effect on haemostasis (88, 90-91). Six studies measured pain but did not find an effect of NSAIDs (16, 65, 73-75, 85, 92), one was inconclusive (85) and 22 studies found an effect of NSAIDs (62-64, 66-72, 75-82, 84-86, 89, 93).

Prior to our study, Ogilvie-Harris (16) performed an evaluation of 6 weeks treatment with naproxen compared to placebo. Pre-allocation disclosure was insufficient and 22 of the 139 case reports were incomplete. Three patients were lost to follow-up. The patients receiving NSAIDs had less pain both at rest and during activity. The NSAIDs group had less synovitis and effusion. A significant number of patients (13/67) in the NSAIDs group had side effects such as heartburn, headaches and gastric upsets.

In 1987, Drez (69) found less post-operative pain comparing a single dose of NSAIDs to propoxiphene plus acetaminophen. The study included 96 patients but only 52 patients had valid pain scores measuring post-operative pain for 6 hours. Two other studies found an effect of a single dose of NSAIDs (66, 89).

Pedersen in 1993 (84) measured the effect of naproxen for 10 days compared to placebo and used a pain score which was a simple addition of each of the days of the first two weeks that had been measured daily using a four-grade scale. There was no difference when the patients were divided into therapeutic and diagnostic arthroscopy. The data were not useable for meta-analysis.

After 10 days treatment with NSAIDs, our study (I) showed a faster regain of quadriceps strength, range of movement and walking without aids compared to the placebo group, without any side effects. Only five other studies evaluated pain on activity (70-71, 76, 84, 86) and four studies evaluating recovery found no effect (71, 82, 84, 89). Smith (89) was not able to detect any difference in recovery between oral NSAIDs, intra-articular bupivacaine and NSAIDs plus bupivacaine. In Nelson's (82) study, two-thirds of all patients returned to work 1 week after surgery with no difference between groups. From the studies by Fasting (71) and Pedersen (84), it was possible to extract data for a meta-analysis together with our study (I). From the studies, number of patients, mean and SD for NSAIDs and placebo were extracted (Table 6.1) and the results are presented in Figures 6.1 and 6.2. Based on the meta-analysis, there is a marginal effect of NSAIDs on days to return to work after knee arthroscopy.

	NSAID	Placebo
Fasting N=244,		
Meniscectomy	115, 17 (11.8)	129, 22 (37.5)
Diagnostic	49, 8.8 (7)	39, 18.4 (17.5)
Pedersen N= 46,		
Meniscectomy	24, 16.3 (16.6)	22, 30 (18.7)
Diagnostic	17, 24.1 (18.7)	24, 25.4 (19.9)
Rasmussen N = 95,		
Meniscectomy	46, 14.9 (3.98)	49, 17.5 (4.34)
Diagnostic N = 25	14, 14.1 (2.66)	11, 19.3 (6.25)

Table 6.1 Data extracted from Fasting (1992) (63), Pedersen (1993) (76) and Rasmussen (1993) (I) for meta-analysis; number of patients, mean and SD.

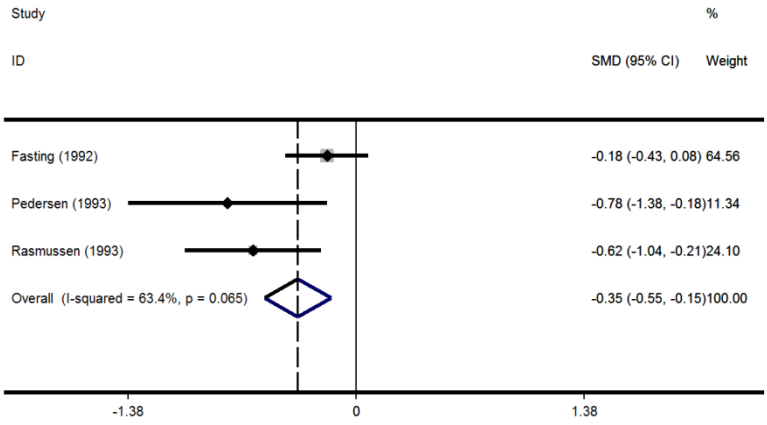

Figure 6.1 Meta-analysis of the effect of NSAIDs versus placebo on days to return to work after arthroscopic knee meniscectomy. Standardised mean difference SMD from 0 (P = 0.001).

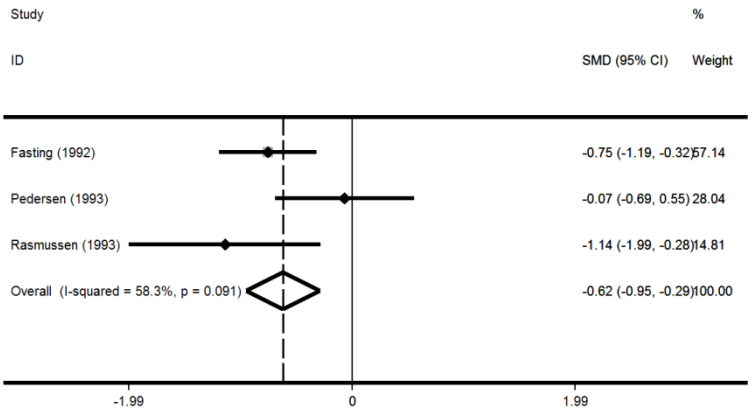

Figure 6.2 Meta-analysis of the effect of NSAIDs versus placebo on days to return to work after diagnostic knee arthroscopy. Standardised mean difference SMD from 0 (P< 0.0001).

Sufficient data that were suitable for a meta-analysis of the effect of NSAIDs versus other analgesics or placebo on pain measured on a VAS after knee arthroscopy were available in twelve studies (66, 69-71, 74, 77-79, 82, 85-86, 89). However, the study by Mardani-Kivi (78) was pre-emptive and hence, excluded. Of the nine studies excluded comparing NSAIDs to other analgesics or placebo on pain found no effect of NSAIDs (64, 72, 84, 92) whereas five did find an effect of NSAIDs (62, 68, 76, 85, 93) indicating there might be some publication bias in favour of studies showing an effect. The meta-analysis shows that when measuring pain shortly after arthroscopy, there is an effect of a single dose whereas the effect is significant but minimal when measuring pain several days after surgery using multiple doses of NSAIDs (Figure 6.3). This indicates that repeated measurement of pain during the first hours and days is more effective as a means to detect a difference.

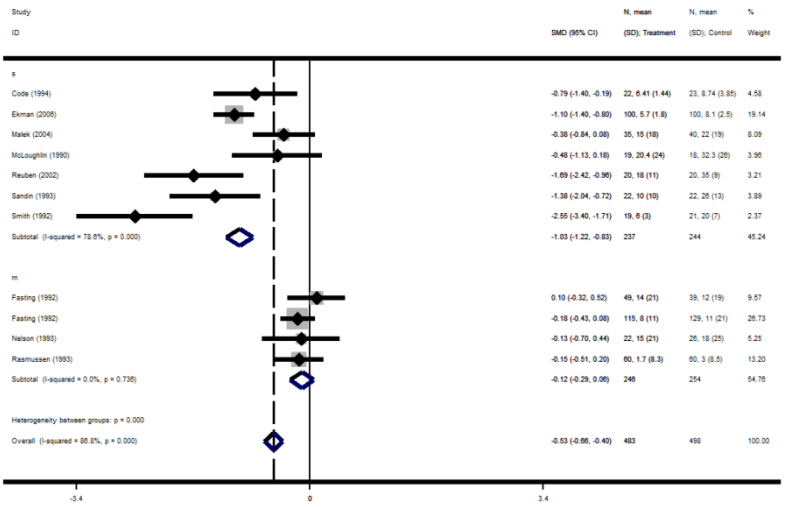

Figure 6.3 Meta-analysis of the effect of NSAIDs versus placebo on pain after knee arthroscopy. The significance tests of standardised mean difference for single dose studies (s) and multiple dose studies (m) was $P < 0.0001$ and $P = 0.2$ respectively, and overall, $P < 0.0001$.

A meta-analysis of randomised controlled trials of the use of post-operative acetaminophen revealed a morphine sparing effect but did not reduce the morphine-related adverse effects (94). Another review concluded that acetaminophen provides analgesic efficacy similar to that of NSAIDs following major orthopaedic surgery

and that acetaminophen may be an alternative to NSAIDs in high-risk patients (55, 85). When using acetaminophen as a rescue analgesic, as in our randomised study of NSAIDs versus placebo, patients in the NSAIDs group did recover faster indicating that it may be appropriate to administer NSAIDs with acetaminophen since these two analgesics may act additively or synergistically to improve analgesia (I).

There is an advantage in adding NSAIDs to patient-controlled analgesia with acetaminophen and morphine (100). The use of NSAIDs was associated with a decrease in the prevalence of post-operative nausea and vomiting and sedation, probably due to reduced use of morphine. Recent studies have demonstrated improved analgesia, shorter hospitalisation times, improved recovery and function, and decreased health-care costs with the use of COX-2 inhibitors in the multimodal management of pain following orthopaedic surgery (97-99), as we have proven in earlier studies (1-4).

NSAIDs - limitations

NSAIDs have a potentially major role in acute pain management because of their primary action in peripheral sites of sensitisation. NSAIDs can provide an effective adjunctive benefit to other analgesic therapy, including opioids and improve outcomes, not only by providing pain relief, but also by sparing patients some of the adverse effects associated with opioid use. Concerns about increased bleeding and inhibited wound healing and bone fusion have limited the use of NSAIDs. Bleeding and wound healing were not found to be a problem in this review of the literature in arthroscopic knee surgery (88, 90-91) and we did not experience any significant complications (I-IV). Most of the studies used unimodal pain treatment. Treatment with NSAIDs alone did not provide sufficient pain relief to allow normal function. Further, most of the literature fails to address the issue of pain during daily function and activity. In multimodal analgesia, it is appropriate to use NSAIDs.

Intra-articular treatment with bupivacaine – efficacy and results

The use of intra-articular administration of local anaesthetics following arthroscopy during the last 2-3 decades has improved post-operative analgesia.

Recent in-vitro studies indicate a toxic effect on cartilage of the most commonly used local anaesthetics: bupivacaine, lidocaine and ropivacaine (100-104). The subsequent reduction in the use of local anaesthetics hampered the multimodal idea of post-operative pain treatment after arthroscopic surgery. A review in 2011(104)

concluded that the use of local anaesthetics may have a detrimental effect on human cartilage and in 2013, a study proved that high-flow infusion increased the risk of glenohumeral chondolysis compared to low-flow (105). Common across these studies is the lack of clinical implications due to exposure to varying concentrations of the local anaesthetics and resultant chondrolysis. The in-vitro studies use anaesthetic directly on the chondrocytes, not taking into consideration the dilution of the anaesthetics due to the use of and residual of 9% saline inside the joint after arthroscopy. Further, the study by Matsen (105) indicates that low-flow and low-concentration of local anaesthetics may not be harmful. A report of 21 cases after a variety of different knee arthroscopic procedures indicated that the use of both high and low-flow-volume pump are related to knee chondrolysis (106). The use of a pump seems to be an additional factor to the toxicity of the local anaesthetic (105-106). Whether or not it is the volume, pressure or flow is not clear.

We did not experience any clinical signs or reports of chondrolysis in the groups involving 80 patients who received intra-articular bupivacaine (II-III). Recent studies within the last 5 years investigating intra-articular bupivacaine (108-114) do not report any incidence of chondrolysis.

Even though bupivacaine is a long-acting local anaesthetic compared to other local anaesthetics, the effect on post-operative pain is short from a clinical point of view. A review evaluating the short-term effect within 4 hours after knee arthroscopy stated there is weak evidence for the use of intra-articular bupivacaine after arthroscopic knee surgery (115). Different operative procedures within the treatment groups and low sample sizes may explain these different results. Further, measurement of pain in activity may have more power to detect a difference (I-IV).

There may be a longer-acting effect of intra-articular bupivacaine and measurement of pain during activity 24 hours after knee arthroscopy may be able to detect a clinical difference.

Intra-articular treatment with bupivacaine – literature review

A search in September 2014 for randomised double blind placebo controlled trials of intra-articular bupivacaine after knee arthroscopy revealed 24 studies (110, 114, 116-141). Up to one third of the studies, did not find an effect on pain score (119, 123, 129, 134, 136, 138-140) or rescue medication (116, 118). Twenty studies were excluded because of a lack of measurements at 24 hours (129, 131), use of regional anaesthesia (117, 137), use of incisional anaesthetic (130), other intra-articular treatment (127) and inadequate data for analysis (110, 116, 118-123, 133, 135-136, 139-141). Mean and SD of pain intensity on VAS were extracted from tables and figures. Only four studies measured pain in activity 24 hours after knee arthroscopy

(114, 124-126) whereas five measured pain at rest 24 hours after arthroscopy (128, 130, 132, 134, 138) (Figure 6.4).

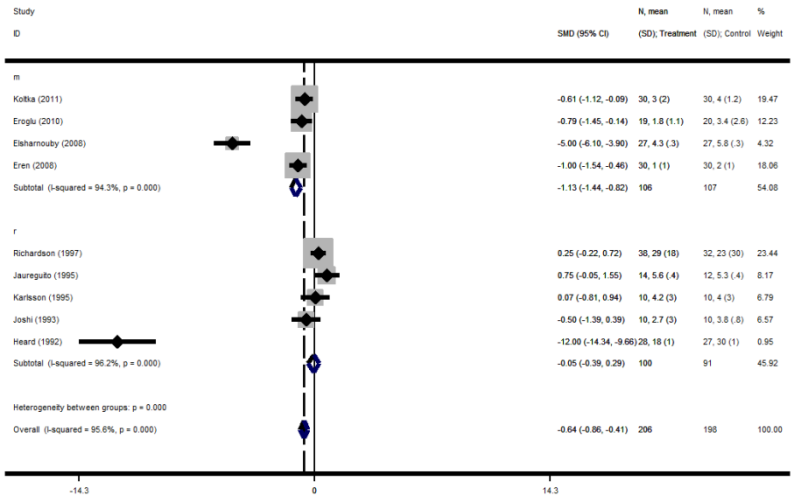

Figure 6.4 Meta-analysis of the effect of bupivacaine versus placebo on pain during motion or at rest 24 hours after knee arthroscopy. The significance tests of standardised mean difference for pain during motion (m) and pain at rest (r) was P < 0.0001 and P = 0.7) respectively, and overall, P < 0.000).

The analysis finds a relevant effect of bupivacaine 24 hours after knee arthroscopy when measuring pain during motion. This is in accordance with the 10-day pain profiles during activity in our studies (II-III). It may be due to a longer-acting neural response to local administration of anaesthetics.

Intra-articular treatment with morphine – efficacy and results

Before our studies (II-IV), application of intra-articular morphine proved the activation of peripheral opioid receptors in inflammation (20). We showed a longer effect of morphine combined with bupivacaine on pain, activity and inflammation demonstrating a prolonged analgesic effect beyond 24 hours (II-III). A review based on the author's own two studies and seven other studies out of a total of 67 randomised trials concluded there is no effect of intra-articular morphine (142).

Another review of 27 of 31 trials indicated that 5 mg of intra-articular morphine provides pain relief up to 24 hours when there is a minimum of 30% of maximum pain intensity (143). A third review (144) concluded that intra-articular morphine has a definite but mild analgesic effect. These reviews based their conclusions on 9 (142), 25 (143) and 27 (144) randomised controlled trials respectively. Different validity criteria and methods of analysis have been used and surprisingly with an decreasing amount of included studies over time!

The conflicting results of the reviews may be due to morphine having a better analgesic effect when there is a higher inflammatory response. One study concluded that for surgeries with a higher inflammatory response, intra-articular morphine has a better analgesic effect (145). A longer reduction of post-operative pain beyond 24 hours due to injection of morphine together with bupivacaine, as in our studies (II-III), supports the hypothesis of peripheral opioid receptor activation in inflammation. This judgement that intra-articular morphine can provide long-lasting effective post-operative analgesia is a confirmation of the hypothesis by Stein (20).

Intra-articular treatment with morphine – a literature review

To ensure a baseline for pain and intra-articular inflammation, studies on meniscectomy or cruciate ligament reconstruction alone were appropriate to be included in a review of the literature. A search in September 2014 for randomised trials comparing morphine to placebo found nine studies (126, 145-152). Mean and SD of pain intensity on VAS was extracted from tables and figures. Measurements beyond 1 day were obtained from three studies (146 (3 days), 147 (7 days), 150 (4 days)). Meniscectomy was performed in eight studies (126, 145-149, 151-152) and ACL reconstruction in three studies (145, 150, 152) (Figure 6.5).

The analysis finds that morphine does have an effect when there is indication for meniscectomy or reconstruction of the anterior cruciate ligament. The effect is beyond 1 day and up to 7 days after surgery and relates to the pre-operative baseline pain and possible inflammation. This is consistent with our findings (II-III) and the measurements of the inflammatory response (II). This is also in accordance with the theory of the possible action of local analgesics on the surgical stress response either by a local anti-inflammatory or neuro-endocrine response. A possible systemic effect of intra-articular morphine may be negligible since the dose is 1-2 mg.

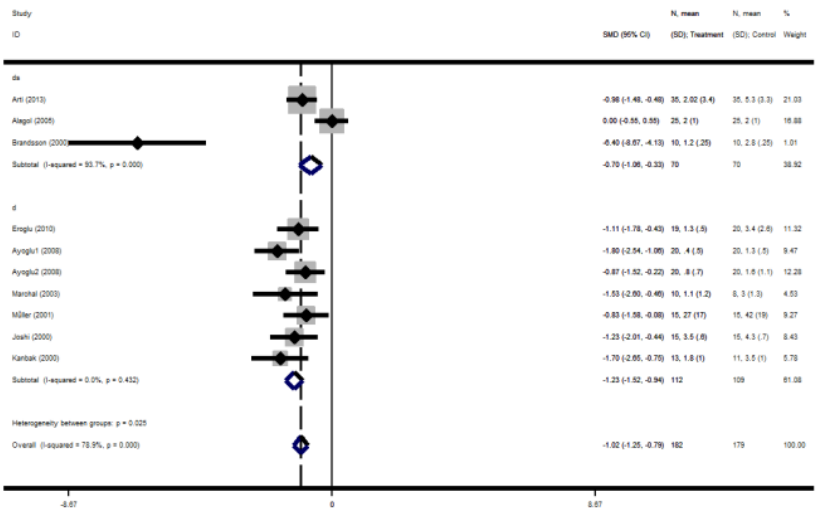

Figure 6.5 Meta-analysis of the effect of morphine versus placebo on pain 1 day (d) or several days (ds) after knee arthroscopy. The significance tests of standardised mean difference for pain at 1 day (d) and pain at several days (ds) was P < 0.0001 and P < 0.0001 respectively, and overall, P < 0.0001.

Intra-articular treatment with corticosteroid – efficacy and results

In the management of convalescence and pain after orthopaedic surgery, the potential value of corticosteroid treatment has received increasing attention especially within arthroscopy (II-IV, 52, 153-159), arthroplasty (160-175), and spine and other orthopaedic procedures (4, 176-181) during the last decade.

The reported benefits of corticosteroid treatment are reduced pain, time of immobilisation and duration of convalescence. In arthroscopic knee surgery, intra-articular (II-IV, 154, 156, 159, 182) and peroral (52, 158) treatment with corticosteroid has been reported as having some anti-inflammatory effect. In other surgical procedures, a pre-operative single dose of corticosteroid resulted in a reduced inflammatory and pain response (183).

The risk of complications such as septic arthritis reduces the potential of corticosteroid to enhance recovery. The risk of infection may increase after a single dose of glucocorticoids, especially after orthopaedic surgery. However, an attempt to evaluate the potential risks after hip and knee surgery failed due to small sample sizes and clinical heterogeneity (168).

The annual incidence of septic arthritis in the general population is 0.02 to 0.05 per 1000 (184). After knee arthroscopy, the risk of septic arthritis is 0.8 per 1000 and steroid injections prior to arthroscopy for degenerative changes may increase the risk to 2 per 1000 (185). After paediatric and adolescent knee arthroscopy, the incidence is 3 per 1000 (186). Post-operative infection rates in recent studies are from 0.02% to 1.13% (185-193). They report 433 infections after 542,394 (0.08%) arthroscopic procedures.

A single dose of intra-articular corticosteroid may increase the risk of avascular bone necrosis and synovitis, or have an effect on cartilage. There is no side effect reported following single dose administration of corticosteroid in other surgical procedures (183). There is a benefit of intra-articular steroids in the treatment of osteoarthritis in reducing oedema, inflammation and pain (194-195).

In an attempt to perform a safety study of intra-articular steroid after knee arthroscopy regarding an infection rate of 0.08%, a very large number of patients is needed, thereby making it impractical. If randomising 2000 patients to steroid or no steroid, the power to see a double risk of infection would only be 7.4%! Still there is a need to perform a safety study to reach some kind of a consensus.

Intra-articular treatment with corticosteroid – literature review

In two randomised studies, we were the first to investigate the effects of intra-articular steroid after knee arthroscopy and to report a long-term effect on pain, function and inflammation (II-III). Four other studies have shown an effect on pain within 24 hours (154-155, 159, 182) and one up to 6 weeks after knee arthroscopy (156). Consensus is still lacking on whether corticosteroid offers clinically relevant benefits after arthroscopic surgery (II-IV, 154-155, 159, 182). A major reason for the lack of consensus is the potential risk of increased incidence of septic arthritis after arthroscopy. Septic arthritis should be an infrequent occurrence after arthroscopic surgery. In the six randomised trials after arthroscopic knee surgery, no infection occurred in 129 patients receiving intra-articular steroid (II-IV, 154-155, 159, 182) (Figure 6.7). Pain profiles 24 hours after surgery were not significant in favour of steroid in two studies both including meniscectomy (II, 182). A possible explanation may be greater surgical trauma compared to the inclusion of diagnostic and other minor procedures in the other studies.

There may be a systemic effect of intra-articular glucocorticoids due to the high doses and slow release. It may explain the long-lasting analgesic effects.

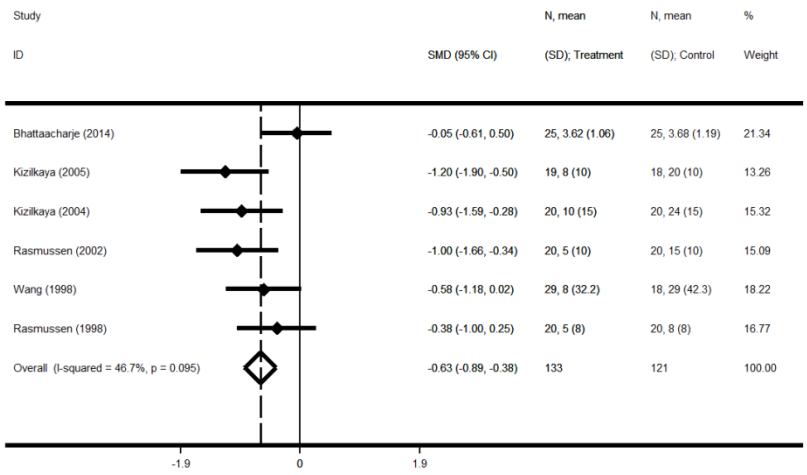

Figure 6.7 Meta-analysis of the effect of glucocorticoid versus placebo on pain 24 hours after knee arthroscopy. The significance test of standardised mean was P < 0.0001.

The mechanism of action of intra-articular steroid in arthroscopic surgery is on the cellular level binding to the nucleus and by altering transcription. This reduces the amount of lymphocytes, macrophages and mast cells (196-197). In turn, phagocytosis, lysosomal enzyme release, and the release of inflammatory mediators are inhibited (198). Finally, the reduction in release of interleukins, leucotrienes and prostaglandins reduces inflammation and pain (199).

Tourniquet

The use of a tourniquet has obvious benefits to the surgeon. The advantages are a relatively bloodless field, improved surgical visualisation and diminished operating time. The pathophysiological effects of tourniquet use are noxious stimulation

(alterations in neural function, hyperalgaesia, ischemic pain), direct tissue compression, haemodynamic effects (reactive hyperaemia, post-operative haematoma, post-anoxic oedema) and micro vascular abnormalities (increased platelet adhesion, decreased endothelial cell function) (200-209). The risks are nerve paralysis, vascular injury, swelling, stiffness, delay in recovery of muscle power, changes in circulatory volume, limb hyperaemia on release of the tourniquet, potential cardiac or respiratory complications in patients with a poor cardiac reserve, and increased risk of deep-venous thrombosis. The possibility of so many complications contributes to the controversy about tourniquet use.

There is poor knowledge of soft tissue damage due to tourniquet use. Measured by serum creatinine phospokinase, tourniquet use for less than 30 minutes seems safe (210). The ischemic changes in the skeletal muscle have been measured using microdialysis (211). The changes were also found in arthroscopic ACL reconstruction, where surgical trauma is not as severe as in total knee arthroplasty (211).

In an additional analysis comparing the results where a tourniquet was used (I) compared to the results where tourniquet was not used (II-III), we found a negative effect of the tourniquet. The signs were clinically relevant regarding muscular strength, effusion and range of motion. Regarding outcomes, the patients reported a longer duration of time before return to work and increased pain.

In a randomised study, we found improved knee range of motion, reduced pain and improved patient-reported outcome when not using the tourniquet in total knee arthroplasty (6). Two other recent randomised studies have reported the same results (212-213). Several randomised studies and meta-analyses have been published (6) and disagreements still seem to remain (218). The recent studies clearly demonstrate the benefits of not using a tourniquet. Not using a tourniquet may improve the effect of multimodal pain treatment in arthroscopic surgery.

The surgical trauma

From the additional analyses of data from our studies (I-III), it is obvious that increasing degrees of surgical trauma challenge the efficacy of the multimodal pain treatment.

In 1916, Crile described the relationship between the degree of surgical trauma or tissue damage and the amount of acute pain and long-term post-operative pain (215). He advocated for a multimodal approach with the use of regional analgesia in addition to general anaesthesia, and even suggested pre-emptive analgesia to reduce post-operative morbidity (215). Post-operative persistent pain, now referred to as

central sensitisation, is both a neuropathic and inflammatory pain reaction (Figure 1-3). It is an increased pain sensitivity described as hyperalgaesia and tactile allodynia, where there is persistent chronic pain and pain to light touch. Further, there is a reduction of efferent inhibitory transmission (217-217).

The surgical trauma changes the excitation threshold of the peripheral and central neurons and increases the nociceptive afferent pathways. This may lead to persistent post-operative pain or central sensitisation of pain (218-220). Despite the advances that have been made in understanding pain, up to half the patients nevertheless still experience moderate to severe pain following surgery (220-222).

Even though the presence of inflammation activates opioid receptors, not only post-operative intra-articular morphine, but also pre-emptive intra-articular morphine does have an effect in a multimodal approach for arthroscopic meniscectomy (223). In arthroscopic-assisted acromioplasty and rotator cuff repair, a combination of intra-articular morphine, methylprednisolone and ropivacaine administered pre-emptively, intra- operatively and post-operatively were superior to patient-controlled post-operative analgesia (224).

Abdominal surgeons were the first to document the value of multimodal or balanced analgesia (225). In a series of studies, we incorporated multimodal analgesia, using a combination of analgesics throughout the peri-operative period to control nociceptive and centrally stimulated pain (1-4). A better understanding of pain mechanisms and surgical stress response has encouraged the development of this multimodal strategy with the use of pre- and post-emptive analgesics, NSAIDs and continuous epidural and intra-articular treatment. Furthermore, we incorporated substantive pre-operative information, stress reduction, early active mobilisation and oral protein supplementation. The stress reduction included a substantive revision of peri-operative care programmes, peri-operative external heating, low volume therapy, reduced blood transfusion, oxygen supplementation, reduced use of opioids and minimal invasive surgery. This concept of multimodal intervention improved analgesia, reduced opioid-related adverse events, reduced complications, reduced hospital stay and improved rehabilitation and recovery. A part of the rationale for this strategy is the achievement of sufficient analgesia due to the additive or synergistic effects of the different analgesics. This allows a reduction in the dose of these drugs and thus a lower prevalence of adverse effects.

This management strategy of employing multimodal and pre-emptive approaches, with an emphasis on preventing algesic flare prior to surgery and moderating or preventing development hyperalgesic states after surgery, has been proven to reduce hospitalisation, complications and chronic pain and increase patient outcomes (1-4).

Several other studies have used this understanding of the surgical trauma to implement and document the effect of multimodal pain treatment in arthroplasty (226-228) hip fracture (226, 229-230) and spinal surgery (231).

6.4. METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

Because of differences in methods applied in studies examining the effect of analgesia on pain after arthroscopic surgery, it is difficult to compare the results. Measurement of pain involves the use of 100 mm VAS or a range of other Likert scales, at different time points and in varied activities or at rest. Furthermore, the presentation of data can vary with the use of mean, SD and SEM, or median and range, and different graphic presentations. In addition, different endpoints, follow-up times, and statistical methods are used. Even in this literature review, it was difficult to interpret and compare results. The strength in the studies of intra-articular treatment in knee arthroscopy (II-III) was that we adjusted for the confounding of different surgical procedures experienced in the study of oral NSAIDs (I) and used activity-specific pain measurements. Another strength was the use of a consistent methodology in data management and analysis of results (II-IV).

A limitation of the study of oral NSAIDs (I) was the different arthroscopic procedures which led to a post hoc subgroup analysis with different small sample sizes and hence a lower statistical power. The difference in the number of operative and diagnostic procedures, however reflects the unselected flow of patients and increases the external validity of the study. Moreover, the additional analyses performed in this review adjust for the confounding of operative and diagnostic arthroscopy. Another limitation was the repeated measurement of pain, not specified or related to rest or activity (I). The following studies used repeated measurement of pain related to a specific activity (II-IV).

In the studies of intra-articular treatment in knee arthroscopy (II-III), the patients were highly selected, either meniscectomy or diagnostic, allowing a smaller group sample size. The internal validity therefore is high, but the external validity is low. Further, the use of three and not two groups makes the interpretation of the results difficult. The translation of the methods into general practice from each study alone may be difficult. The combined analyses of the data and interpretations of the results when compared with the literature increase the evidence for multimodal pain management.

In the study of intra-articular treatment in ankle arthroscopy (IV), we included debridement for impingement and excluded ankle instability, thereby excluding more than one-third of eligible patients and reducing the external validity. Further, we experienced one deep infection that, in accordance with a risk incidence of deep

infection at 1-2% after ankle arthroscopy, hampers the use of intra-articular glucocorticoids in ankle arthroscopy.

When analysing the repeated measurements of pain after intra-articular treatment (II-IV), we used the repeated measures analysis of variance test described by Matthews (48). When using this mixed effects model, taking treatment, time and change over time into consideration, we did find a level of significance. This is a very important finding and strengthens the importance of choosing an appropriate statistical package and the use of statistical advice when designing a study.

These four studies and associated reviews of the literature indicate that there is a need for a better tool to measure the efficacy of pain treatment. Use of sufficient rescue medications in a well-designed setup usually finds no difference in pain on VAS. A priori, most patients will use rescue medications up until VAS < 30, so it is to be expected that there is likely to be no difference in VAS between the groups. However, analysis of the literature shows that this is not the result. Some studies either find no effect of rescue medication on VAS measured pain or find the opposite by suggesting an important relation between rescue medication and pain measured by VAS. Few studies have used time until first rescue medication as an outcome measure. From a study design perspective, it is possible to overlook an effect or to postulate an effect, when using only one of those methods and not measuring rescue medication and pain simultaneously (Figure 6.8).

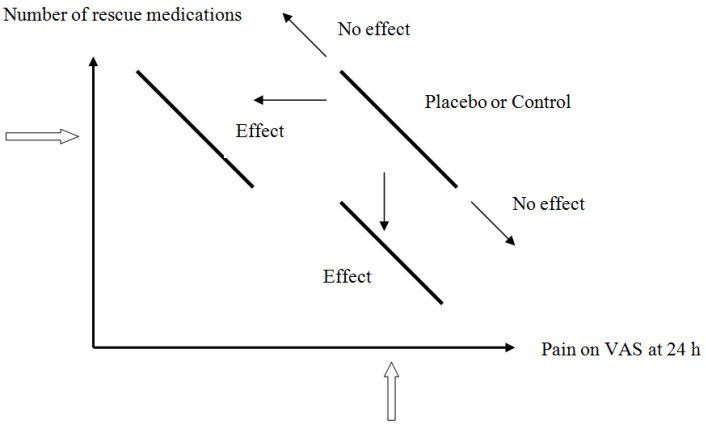

Figure 6.8Measuring efficacy using rescue medication or pain on VAS. It is possible in both methods to overlook an effect or postulate an effect when not measuring rescue medication and pain on VAS simultaneously.

In the figure, when plotting medication against pain on VAS, it is apparent how easy it is to postulate a significant difference in VAS when not considering use of rescue medication. In an intervention group, there might be a significant reduction in pain on VAS but an unrecognised increase in the use of rescue medication as indicated by the “no effect” arrow. This can explain the difficulties in evaluating the efficacy of intra-articular morphine after arthroscopic surgery. Statistically, a regression analysis of the difference between the groups will reveal the answer.

A repeated time to event analysis (232) including a pain measure and time interval between rescue doses may be a proper or better tool to measure pain management.

CHAPTER 7. FUTURE RESEARCH

Peri-operative use of NSAIDs in orthopaedic surgery may impair wound and bone healing. This common interpretation of the current literature, to some degree, hampers the use of peri-operative NSAIDs, even in minor surgery such as arthroscopy. However, there is no evidence for an association between use of NSAIDs and bone healing. We have continued research in the use of NSAIDs and are conducting a double blind placebo-controlled study of NSAIDs on bone healing after distal radial fracture. To investigate whether NSAIDs reduce fracture healing, we are measuring bone density, bone composition, bone markers and clinical outcome.

The intra-articular use of bupivacaine is toxic for the cartilage in animal studies and in human shoulder arthroscopy. In animal studies, standard concentration of bupivacaine is damaging to cartilage cells. It is necessary to investigate the safety of bupivacaine inside the knee joint after arthroscopy. Compared to animal studies, the concentration of bupivacaine may be lower than expected due to the use of saline during arthroscopy. Recently, we have investigated a slow release preparation of bupivacaine. We found a reduction in postoperative pain and morphine consumption up to 72 hours after soft tissue and bony surgeries. (Presented at the annual meeting of the American Society of Anaesthesiologists; October 11-15, 2014; New Orleans, Louisiana). Another analgesic for possible use after knee and other small joint arthroscopy is topical lidocaine. Two pilot randomised placebo-controlled studies indicate a reduction of escape medication after short duration knee arthroscopy (Presented at EFORT May 23-25, 2012. Berlin). We plan a larger placebo-controlled study after meniscal suture or resection. It is necessary to investigate the analgesic effectiveness of intra-articular morphine in placebo-controlled design after plica resection and meniscectomy using repeated time to event analysis of escaped medication. A study with 1000 patients in each of two groups can address the safety of intra-articular steroids after arthroscopy.

We are investigating the use of a tourniquet in total knee arthroplasty in a randomised controlled study. We are measuring local stress response with microdialysis and the stability of the implant with roentgen stereo metric analysis. We are investigating the benefit of minimal invasive surgical technique in lumbar spinal fusion. In a randomised controlled trial, minimal invasive surgical technique reduced length of stay and pain. The long-term safety, efficacy and cost-benefit are currently being monitored. Microdialysis is used to monitor the local and general surgical stress response and a computer model is used to monitor preservation of muscular function. The analysis of the impact of the surgical trauma on outcome indicates there is a need for monitoring the stress response in relation to the efficacy of multimodal pain treatment. We have planned a study using microdialysis to

monitor the stress response and repeated time to event analysis of escape medication in arthroscopic knee surgery. The capacity of a single dose steroid or other analgesics such as pregabalin, gabapentin, fentanyl, local anaesthetics, NSAIDs and paracetamol, to reduce the surgical stress response and the duration of convalescence can be addressed in this setup.

CHAPTER 8. CONCLUSIONS

NSAIDs for 10 days improve recovery after operative and diagnostic knee arthroscopy. The patients demonstrated a faster return to work. In the actively treated group, there was improved range of motion, less effusion, increased activity and less pain. The results showed better recovery over time. The effect is probably more to accelerate recovery than to increase the level of recovery achieved. When performing meniscectomy or other arthroscopic procedures, there were significant effects of NSAIDs whereas the effects of NSAIDs were minor after diagnostic arthroscopy. This indicates that the benefits of NSAIDs are related to the severity of, and the reduction of, the inflammatory response to surgical trauma. Further, the study demonstrates the primary outcome measure for evaluating modulation of the stress response should be degree of activity.

NSAIDs have a potentially major role in acute pain management because of their primary action in peripheral sites of sensitisation. NSAIDs can provide an effective additional benefit to other analgesic therapy including opioids and improve outcomes, not only by providing pain relief, but also by sparing patients some of the adverse effects associated with opioid use. Concerns about increased bleeding and inhibited wound healing and bone fusion have limited the use of NSAIDs. However, 10 days treatment with NSAIDs without any side effects provides a faster return to work and restoration of normal activity.

The main finding of intra-articular treatment in knee arthroscopy was a faster return to work by the addition of intra-articular methylprednisolone. Since joint effusion and acute phase response protein were reduced or eliminated, the mechanism may be anti-inflammatory. This potential to accelerate recovery must be weighed against the risk of complications. The reduction of the inflammatory response may theoretically alter wound healing. However, there is no clinically relevant wound to heal following knee arthroscopy and the inflammatory response may, in this type of operation, be considered an unwarranted response. Another potential complication is infection that seems to be negligible after a single dose.

Another finding was the combined effect of bupivacaine and morphine, and the combined effect of bupivacaine, morphine and methylprednisolone on time taken to return to work. Both were shown to provide a faster return to work. Further, there was improved range of motion, improved muscular strength, reduced synovial effusion, increased activity and less pain.

In ankle arthroscopy, the combined use of intra-articular bupivacaine, morphine and methylprednisolone is rational and effective in reducing pain and inflammation. The treatment had a pronounced and clinically relevant effect and provided a faster

return to work after arthroscopic ankle debridement. However, infection occurred in one of the members of the intervention group. Since purulent arthritis may have severe consequences, there is a need for large studies to investigate intra-articular treatment with glucocorticoids compared to the usual incidence of infection.

An additional analysis of the study of oral NSAID and of intra-articular treatment after knee arthroscopy revealed the detrimental effect of surgical trauma on time taken to return to work and outcome.

Comparing the study of oral NSAIDs after knee arthroscopy to the studies of intra-articular treatment in knee arthroscopy, we found that avoiding the use of a tourniquet provides a faster return to work, improves range of motion and muscular strength, and reduces synovial effusion and pain.

In the four trials, we have demonstrated a shorter duration of convalescence of several days with a reduction in time to return to work after knee and ankle arthroscopy with the use of oral NSAIDs combined with bupivacaine plus morphine or combined with bupivacaine, morphine plus steroid.

Multimodal pain treatment after arthroscopy of the knee and ankle using NSAIDs and intra-articular bupivacaine, morphine and methylprednisolone reduce the time taken to return to work by more than 50% or up to 8 days. Use of a tourniquet and the degree of surgical trauma to some extent reduce the effect. There is a need for future trials to monitor the stress response to surgical trauma in relation to the efficacy of multimodal pain treatment.

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SUMMARY

The thesis is based on four randomized controlled trials. The main hypothesis was that multimodal pain treatment provides faster recovery after arthroscopic surgery.

NSAID was tested against placebo after knee arthroscopy. Intraarticular bupivacaine plus morphine plus steroid was tested against bupivacaine plus morphine and against saline in two trials after arthroscopic knee meniscectomy and diagnostic knee arthroscopy respectively. Intraarticular bupivacaine plus morphine plus steroid was tested against saline after operative ankle arthroscopy.

Oral NSAID reduced time to work from 17 to 14 days after knee arthroscopy. Intra-articular treatment with bupivacaine plus morphine and bupivacaine plus morphine plus steroid after arthroscopic knee meniscectomy reduced time to work from 10 to 5 to 3 days. Intraarticular treatment with bupivacaine plus morphine and bupivacaine plus morphine plus steroid after diagnostic knee arthroscopy reduced time to work from 10 to 5 to 2 days. Additional analysis revealed that the surgical trauma and the use of tourniquet influenced recovery.

The thesis proves a reduction in the time to return to work after knee and ankle arthroscopy with the use of oral NSAIDs combined with bupivacaine plus morphine or combined with bupivacaine, morphine plus steroid.

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